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TREATMENT OF DEPRESSION IN PATIENTS WITH OSTEOARTHRITIS: THE IMPORTANCE OF AN EARLY DIAGNOSIS AND THE ROLE OF DULOXETINE

Cátia Jesus[1], Inês Jesus[1] & Mark Agius[2]

[1]Charles University in Prague, Third Faculty of Medicine, Prague, Czech Republic
[2]Clare College Cambridge, Department of Psychiatry University of Cambridge, Cambridge, UK

SUMMARY

Background: *Osteoarthritis (OA) also called degenerative joint disease is the most common chronic condition of the joints that just in 2004, caused moderate to severe disability in 43.4 million of people. OA in Western populations is one of the most frequent causes of joint pain, loss of function and disability in adults. In the U.S. it is the second most common cause of work disability in men over 50 years of age, following ischaemic heart disease, and accounts for a higher number of hospitalizations when compared with rheumatoid arthritis (RA) each year. This condition is associated with chronic pain (which can be severe in many cases) and long term inflammatory processes which all together represent conditions that are known to be associated with depression. Depression is among the most burdensome disorders worldwide having affected just in 2010 15.4 million adults worldwide. Depression is associated with increase of symptom burden, greater level of functional impairment and increased risk of both disease complications and mortality. With this research we wished to put in evidence the importance of an early diagnosis of Depression in patients with osteoarthritis by using PHQ9 and suggest Duloxetine as an antidepressant that can be helpful in the management of not only pain but also depression in OA patients.*

Methods: *Our study is a literature based research.*

Conclusion: *Early Diagnosis of depression of patients with osteoarthritis appears to be crucial for improving the outcomes of patients with OA and that can be easily and efficiently done with PHQ9. Duloxetine presents itself as an ally in the fight against the evolution of depression in patients with OA and should be considered even in mild to moderate states of depression.*

Key words: *Osteoarthritis – depression - PHQ9 – antidepressants - Duloxetine*

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INTRODUCTION

Osteoarthritis (OA) is recognized as one of the most prevalent chronic musculoskeletal diseases worldwide (World Health Organization 2002). The joints typically affected are located in the hands, knees, hips, and spine with varying degrees of joint deformity and swelling (Sarzi-Puttini 2005). Usually beginning when adults are in their 40s, it is estimated that 9.6% of men and 18% of women over 60 years of age are affected with symptomatic OA. Since age is a significant risk factor in its development, it is predicted that OA will be the fourth leading cause of disability by 2020 (Sarzi-Puttini et al. 2005 Woolf & Pfleger 2003) due to the increase of Life expectancy. In fact, the prevalence of knee OA has been reported to be 44% in those who are 80 years old or greater (Felson et al. 1987). The strong correlation between pain and psychiatric distress is not any novelty (Bao 2009) and is pretty clear by now that emotion has a moderating effect on pain (Villemure 2002). Osteoarthritis is the most prevalent cause of chronic pain in older adults, and is often comorbid with other long term conditions such as depression. Depression and painful physical symptoms are known to increase the costs as they leads to an increase/overutilization of healthcare services (Sheehan 2002). One of the biggest problems we are facing nowadays is that conditions such as depression and chronic pain remain under-prioritised, under-detected and under treated (Tan et al. 2015) leading to an increase in symptom burden, greater level of functional impairment and increased risk of both disease complications and mortality (Katon 2012). Some of the barriers to managing depression in people with long term conditions in primary care include the lack of time of the physicians, cultural barriers, inadequate resources and the practioner skills (Coventry 2011). Our study had two main goals: the first one consisted in providing a suggestion to easily detect Depression in patients with OA (even in early stages), the second goal was to determine which antidepressive drug would be the best one for the treatment of depression and the benefits of an early treatment of depressive symptoms with antidepressives in such patients.

Psychological factors such as emotions and beliefs about pain and coping mechanisms have been found to play an important role in an individual adjustment to chronic pain. When pain persists over time, a person may avoid doing regular activities for fear of further injury or increased pain. This can include work, social activities, or hobbies. As the individual withdraws and becomes less active, their overall physical conditioning may decline. This can contribute to the belief that one is disabled. As pain persists, the person develops negative beliefs about their experience of pain or negative thoughts about themselves. These types of thoughts, along with decreased participation in enjoyable and

reinforcing activities, can lead a person to become depressed and anxious. All of these things can fuel and maintain the pain cycle (Figure 1).

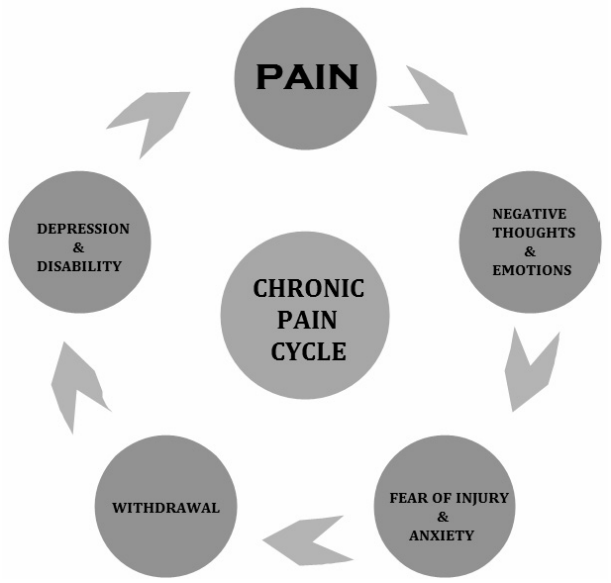

Figure 1. Chronic pain cycle in the origin of major depression disorder

PATIENT HEALTH QUESTIONNAIRE (PHQ9): AN EASY AND EFFICIENT TOOL TO DETECT DEPRESSION IN PATIENTS WITH OSTEOARTHRITIS

Depression is known to lead to the deterioration in social and occupational functioning with reduction of activity levels as well as increased pain behaviour and use of medical services and that's why it should be regularly screened among patients with chronic pain (Pool 2009). Patient Health Care Questionnaire (PHQ) is an instrument for making criteria-based diagnosis of depressive and other mental disorders commonly encountered in primary care (Kurt 2001). PHQ9 improves the detection of depression, assessment of severity (mild, moderate and severe) and is also very useful in guiding treatment decisions. Brevity is as likely to be valued attribute when it comes to assessing depression severity as is when establishing depressive diagnosis (Kurt 2001). PHQ9 is a three page questionnaire that can be entirely self-administered by the patient. In 85% of cases clinicians required less than 3 minutes to review responses on the full 3 Page PHQ (Spitzer 1999). PHQ9 also allows monitoring the response to therapy by being done on a regular basis in each outpatient visit.

COMPARATIVE ANALYSIS BETWEEN DIFFERENT ANTIPSYCHOTICS

One of the goals of our study was to determine which antidepressant had the best overall effect in patients suffering from Osteoarthritis, and before we came to the suggestion of Duloxetine as one of the best choices for this condition there was the need to perform a comparative analysis, between the different types of the most widely prescribed antidepressant drugs.

Selective Serotonin Reuptake Inhibitors (SSRIs) and Tricyclic antidepressants (TCAs): Comparative analysis

Tricyclic antidepressants and selective serotonin reuptake inhibitors are equally effective in the treatment of moderate depressive disorders (Cvjetkovic-Bosnjak et al. 1999). Nevertheless Selective Serotonin Reuptake Inhibitors have replaced TCAs as the drugs of choice in the treatment of depressive disorders, and there are few reasons that can help us understand why. When considering the mechanism of action Tricyclic antidepressants work by increasing the levels of neurotransmitters serotonin and norepinephrine in the brain by slowing the rate of reuptake (reabsorption) by nerve cells. However, the TCAs also block histaminic, cholinergic, and alpha1-adrenergic receptor sites, and this lack of selectivity is what leads for the undesirable side effects such as weight gain, dry mouth, constipation, drowsiness, and dizziness. SSRIs on the other hand are highly selective: they act as weak inhibitors in the reuptake of non-serotonergic neurotransmitters such as norepinephrine, but act as strong inhibitors in the reuptake of serotonin and because of this selectivity, there are fewer side effects associated with SSRIs. As a conclusion is fair to say that The SSRIs have a better overall tolerability profile than the TCAs in both acute and long-term treatment (Peretti 2000).Another advantage that the SSRIs have over tricyclics is that Patients treated with SSRIs have lower rates of treatment discontinuation (Anderson 2000, MacGillivray 2003). Regarding the costs, the overall treatment costs with SSRIs are no greater than those for TCAs. This is despite the tricyclic antidepressants are less expensive per tablet than the SSRIs (Davis 1996, Peveler 2005). Related to the treatment of painful conditions, the TCA show efficacy in the clinical treatment of a number of different types of chronic pain, notably neuralgia or neuropathic pain and fibromyalgia (Micó 2006, McQuay 1996). The precise mechanism of action in explanation of their analgesic efficacy is unclear, but it is thought that they indirectly modulate the opioid system in the brain downstream via serotonergic and noradrenergic neuromodulation, among other properties (Botney 1983, Benbouzid 2008, de Gardarias 1998). For the treatment of pain or depression related to Osteoarthritis we could not find evidence of any studies results published in PubMed, which suggests that further studies on this area should be performed.

SNRI, Paroxetine and other SSRIs

The studies of the SSRI antidepressants such as Paroxetine (which are a class of drugs that are typically

used in the treatment of major depressive disorder and anxiety disorders) and their potential as analgesics has been conflicting. Of the controlled trials examining SSRIs in the treatment of pain, some found that SSRIs are no better than placebo or are marginally superior to placebo. So when Compared with SNRIs such as Duloxetine, it seems fair to say that SNRIs appear to have better results in improving the overall patient condition, physical and psychological, in patients suffering from Osteoarthritis.

Duloxetine compared to members of the same class, such as Venlafaxine

Venlafaxine (SNRI) is also an effective antidepressant that has a balanced neurotransmitter inhibition profile of 5-HT and NA reuptake, and minimal effects on the muscarinic, histaminergic and adrenergic activity. Due to its function on monoamine neurotransmitters, Venlafaxine is considered to have a similar structure to tramadol, an opioid pain medication used to treat moderate to moderately severe pain that binds to the μ-opioid receptor and also inhibits the reuptake of serotonin and norepinephrine. Several randomized controlled trials examined the effect of venlafaxine compared with tricyclic antidepressant and placebo in treating painful polyneuropathy and demonstrated that venlafaxine was superior to placebo and was comparable to TCA in reducing the persistent, sudden and violent outbursts of pressure-evoked pain. In a single-blind placebo run-in trial to test Venlafaxine for Osteoarthritis Pain relief, performed by the Department of Psychiatry and Behavioral Sciences of Washington University, showed that Venlafaxine significantly reduced pain intensity but marginally improved self-reported function. For the treatment of Major Depression, the efficacy of venlafaxine has been established by a number of placebo-controlled studies (Schweizer 1991, Cunningham 1994, Clerc 1994). The comparison of duloxetine and venlafaxine in the treatment of patients with major depressive disorder concluded that there were no significant differences between the two at the end of 6 or 12 weeks, nor were there significant differences between treatment groups on Drug efficacy (Perahia et al. 2008). From a safety perspective, significantly more venlafaxine-treated patients (n=4) than duloxetine-treated patients (n=0, P=0.047) experienced sustained elevations of systolic blood pressure during the fixed dosing period. Otherwise, there were few significant differences in safety measures found between treatment groups during 6 and 12 weeks of therapy (Perahia et al. 2008). When it comes to compare Duloxetine and Venlafaxine is fair to say that there are more similarities than differences. Several clinical studies found no difference in therapeutic effect between the two drugs. However, the major difference between Duloxetine and Venlafaxine is that the former is available as a low-cost generic while the latter is still enjoying patent protection and associated pricing power (Perahia et al. 2008).

DULOXETINE: TREATMENT OF PAIN AND DEPRESSION

Duloxetine is a Serotonin-Norepinephrine reuptake inhibitor and its safety has been well characterized in clinical trials in more than 32,000 patients across all indications. Since its first approval in 2004, over 53 million patients have been treated with duloxetine worldwide, accounting for over 19 million patient-years of therapy. Duloxetine has been shown to be generally safe and well tolerated with no new safety concerns identified in the OA population (Brown 2013). This efficacy on the treatment of the pain has been proven to be independent of the age of the patient. The pain inhibition capacity of duloxetine is also hypothesized to be due to a potentiation of 5-HT and NE activity in the CNS (Woolf 2004). Also consistent with previous studies, patients with depression showed increased brain activation to a pain stimulus in several pain processing regions compared to controls. After Eight weeks of duloxetine treatment significantly reduced brain activation to pain stimulus in the previously over active brain areas was seen (Lopez-Sola 2010). These brain functional changes were accompanied by robust clinical improvement in core and somatic depressive symptoms (Lopez-Sola 2010). Also when considering the patients Global impression of change, patients taking duloxetine reported feeling at least much better compared with placebo patients (Frakes 2011). Patients taking duloxetine also revealed to have a significantly greater reduction in paracetamol usage at 16th weeks of treatment (Bou-Raya 2012), which can be considered beneficial in terms of protection of gastric mucosa. When we are talking about depression there is evidence that duloxetine 60 mg QD is effective for the treatment of adult patients with MDD in the short- and long-term phases of treatment (Ball 2013) even in the ones with mild forms of depression (Perahia 2009). Duloxetine also shown to be efficient in the prevention of relapses (Norman 2014).

ADHERENCE: THE IMPORTANCE OF THE RIGHT DOSE IN THE TREATMENT WITH DULOXETINE

Suboptimal treatment adherence is known to be as a significant impediment to the successful treatment of chronic illness. Medication nonadherence is a growing concern to clinicians, healthcare systems, and other stakeholders (eg, payers) because of mounting evidence that it is prevalent and associated with adverse outcomes and higher costs of care (Ho 2009). Indeed, as few as 50% of patients with chronic conditions take their medications as prescribed, and overall the Duloxetine adherence rates that were observed were consistent with these findings (Able 2014). Patients initiating on duloxetine treatment at the recommended level of 60 mg/day were more likely to be adherent than those initiating at doses greater than or less than 60 mg/day.

Studies also show that increasing the dose of duloxetine in older and younger patients, who were are experiencing adequate pain reduction, appears not to provide additional benefit (Micca 2013).

DISCUSSION

There are hundreds of articles published, as well as conferences taken place worldwide about the incidence of depression in patients suffering from long term chronic conditions, however in daily practice we come across a big lapse in the ability of the physicians to do an early detection of this condition. Depression even though has been shown to cause severe worsening of the prognosis and quality of life of the patients as well as increase in costs for the Health Care Systems, is regularly neglected. The symptoms of depression are not always straight forward and easy to identify, especially in a brief outpatient appointment and that is why a regular screening of patients suffering from Osteoarthritis is crucial. Even when mild, depression should not be neglected and should be always properly treated. So far, SNRIs such as Duloxetine and Venlafaxine have been shown to be the most effective treatment for relieving physical pain occurring with depression, but due to high pricing of Venlafaxine and the need of further controlled trials to examine its potential in the treatment of physical symptoms, Duloxetine can be considered the most effective and accessible way to treat patients suffering from depression associated with chronic conditions available.

CONCLUSION

Remission of depression is correlated with improvement in pain (Hamilton 1960). It is clear that depression and OA-related joint pain adversely affect the clinical outcomes and prognosis of patients. Adopting an integrated approach to care may allow effective, opportunistic case-finding and ensure provision of appropriate management of both physical and mental health problems thereby facilitating identification and timely management of these pervasive and deleterious conditions (Tan 2015). When a patient presents with depression and chronic pain, it is important to address both conditions effectively, therefore, there is a clear need to sensitise physicians who take care of patients suffering from Osteoarthritis (and other chronic painful conditions) to also address depression and its consequences. This can be done by using tools, such as the PHQ9, for the early detection and management of this disorder, and in this way improving the outcome of this patients. From all the drugs used in the treatment of chronic pain and concomitant depression, Duloxetine is considered to be the most effective and affordable form of treatment for various types of chronic pain, including physical pain associated with depression.

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Conflict of interest:

Mark Agius is a Member of an advisory board to Otsuka, Japan.

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Correspondence:
Cátia Jesus, MD, PhD
Charles University in Prague, Third Faculty of Medicine
Prague, Czech Republic
E-mail: catia_vicky@hotmail.com