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Pain Remission in a Patient with Ankylosing Spondylitis with Venlafaxine

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Abstract

Ankylosing spondylitis (AS) is a progressive chronic spine condition that is manifested by inflammation that primarily involves the sacroiliac joints. This case report summarizes the diagnosis and the available treatments of AS and then describes a 40-year-old gentleman with AS who experienced a marked decrease in pain when the antidepressant venlafaxine was added during treatment of an episode of major depressive disorder (MDD). The patient wanted to indefinitely maintain venlafaxine treatment for the management of AS associated chronic pain which contributed to his permanent disability and unemployability. The outcome of this single case report is incidental and could not be generalized or implemented as an evidence-based intervention for pain management in AS. Further randomized clinical trials (RTCs) need to be conducted to confirm the beneficial effects of antidepressants in alleviating AS associated pain.

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Introduction

Ankylosing spondylitis (AS) is a chronic, rheumatic disease of the spine which primarily involves inflammation of the sacroiliac joints usually described as sacroiliitis. The inflammation affects the entheses which are the sites of attachment of ligaments, tendons, and joint capsules to bone [1]. In addition to the inflammation, bone erosion and formation of syndesmophytes occur, leading to pain stiffness of the spine and the development of spinal ankylosis [2]. It is considered a lifelong condition, also known as Marie-Strumpell disease or Bechterew's disease [3,4]. It usually starts in the lower back, but can then spread up to the neck, peripheral joints and could progress to bony fusion of the spine leading to the damage of joints in other parts of the body, osteoporosis, and fractures [4]. AS is considered a rare disease with a worldwide prevalence of up to 0.9%, typically affecting young adults with a peak age of onset of 15-35 years and higher incidence in males [5,6]. AS seems to correlate with the histocompatibility antigen HLA-B27 [2]. Genetic studies show more than 90% of patients with AS have inherited HLA-B27 and in North American Caucasians, the prevalence of HLA-B27 is 7%. Of those who have inherited HLA-B27, it is estimated that only 1-6% develop AS [7]. In families of patients with AS, the prevalence may be nearly 30% in first-degree relatives with HLA-B27 [7]. The concordance rate among identical twins is 65%, which supports the presumed genetic component [7]. Several other susceptibility genes have also been identified [2].

Diagnosis

AS is diagnosed based on its clinical presentation, laboratory, and imaging findings. It usually has an insidious onset starting in the lower back. Patients usually present with dull pain in the lower lumbar region or gluteal region. Which then spread up to the neck, peripheral joints and could progress to bony fusion of the spine [4]. They may complain of morning stiffness of the lower back that lasts for a few hours and improves with activity. The pain tends to persist for more than 3 months, and is worsened by rest. Bony tenderness commonly occurs at the costosternal junctions, spinous processes, iliac crests, greater trochanters, ischial tuberosities, tibial tubercles, and heels. Additional findings include synovitis of hips, knees, ankles, and metatarsal phalangeal (MTP) joints. Upper limb joints, except for the shoulder, are almost never involved. Arthritis in the hips and shoulders also could occur. Peripheral arthritis and interior uveitis could also develop. Many patients with AS describe subclinical findings of inflammatory changes in the small or large bowel and some patients with AS have Crohn's disease or ulcerative colitis [8]. Few patients with AS develop aortitis or cardiac conduction abnormalities [9]. The risk of these complications increases with age and can be manifested as a complete heart block, and aortic insufficiency with congestive heart failure. Pulmonary findings in patients with AS include upper lobe fibrosis and extrapulmonary restrictive lung disease from

increased rigidity of the chest wall [10]. Patients with AS may also present with psoriatic lesions [11]. Acute anterior uveitis is considered the most common extra-articular manifestation of AS and can be the presenting symptom of the disease [12].

Treatment

Many patients with severe AS have a poor quality of life, and experience permanent physical disability and loss of productivity [13]. Early identification and treatment are integral to the prevention of worsening and progression of AS. Nonpharmacological treatment modalities such as exercises, physical therapy and hydrotherapy are recommended for both short -term and long -term treatment of AS [13]. Physiotherapy intervention could benefit some patients with AS [14]. Pharmacological treatment with non-steroidal anti-inflammatory drugs (NSAIDs), could benefit some but not all patients with AS. [15]. Multiple RTCs have addressed the efficacy and safety of both nonselective and selective NSAIDs. Gastrointestinal toxicity remains their major side effect, with increased concern about the potential of cardiovascular toxicity, especially with the selective cyclooxygenase-2 inhibitors [16]. Despite the lack of RCTs confirming the efficacy of corticosteroids such as glucocorticosteroids (GCs) and their worrisome multiple adverse effects; local GC injections, could be advisable in some patients with AS [17]. Although the disease modifying antirheumatic drugs (DMARDs) such as sulfasalazine have also been used, no evidence has been yet established to confirm their long-term effectiveness in the treatment of AS [18]. Oral bisphosphonates and intravenous pulses of the bisphosphonate pamidronate have also been investigated and shown clinical improvement only in few studies [19]. The tumor necrosis factor inhibitors (TNFs) such as infliximab (INF), etanercept (ETA), adalimumab (ADA), and golimumab (GOL) could reduce spinal inflammation and have improved AS prognosis in many patients. [20,21]. Although opioid analgesic could be prescribed for patients with AS associated pain who have not responded to other treatment intervention [22], they are not usually recommended due to the increased risks associated with patients likelihood of also using anxiolytic, hypnotic, antidepressant, and muscle relaxant medications which could precipitate problematic adverse effects related to the combination of these medications [23]. Surgery is not usually indicated for the treatment of AS unless the hip joints are damaged and thus requiring hip replacement and, in some patients, spinal surgery may be indicated for segmental instability and for correction of fixed kyphotic deformity [24].

Antidepressants Role in Pain Management

Antidepressants are used as adjunctive treatment for pain conditions. The mechanism of action by which antidepressants relieve pain is unknown but has been attributed to their effects on serotonin and norepinephrine, particularly along the descending spinal cord pain pathways [25]. The effects of antidepressants on pain are reported to be independent of their effects on treating depression [26]. Their efficacy has been also been documented in the treatment of migraine and tension headaches, neuropathic pain, and chronic pain syndromes, including those associated with cancer [27]. The various antidepressants used for pain management are illustrated in table1.The beneficial effects of antidepressants in relieving pain associated with AS have not been confirmed or documented in any current or past RCTs. This case report describes the beneficial effects of venlafaxine on the remission of pain in a 40-year-old gentleman with AS who was initially prescribed this venlafaxine antidepressant for treatment of MDD.

Table1: Antidepressants used for pain management

Tertiary amine tricyclic antidepressants (amitriptyline, doxepin, imipramine	Yes	+++	+++
Venlafaxine	Yes	++	+
Duloxetine	Yes	++	+
Bupropion	Yes	+	+
Secondary amine tricyclic antidepressants (desipramine, nortriptyline	Yes	++	+++
Paroxetine, citalopram	Yes (modest)	+	+
Fluoxetine	No	-	+

High, +++; Moderate, ++; Low, +
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Case Presentation

Mr. S is a 40-year-old gentleman who was diagnosed with AS at the age of 32. He complained of stiffness and pain in the neck, middle back, low back, hips, and upper buttocks. He also had chronic fatigue, coughing and partial loss of his spine mobility. His pain was more pronounced in early mornings and at night. He was adversely affected by the immobility and painful effects of AS and was unable to maintain his employment as a construction worker and subsequently qualified to receive social security disability income. He was single, never married and had no children. He lived alone in a subsidized apartment building and received assistance from visiting nurse and a care giver in regards to his activities of daily living. Because of his difficulties in food preparation and cooking, he depended on daily delivery from meals on wheels. He could not exercise and did not tolerate physical therapy or hydrotherapy. He has been treated with the NSAID celecoxib, with periodic injection of GC. Although the combination of these medications decreased his body stiffness and prevented further deterioration in his spine mobility, he continued to suffer from severe neck, back and hips joint pains. Despite repeated suggestions from his primary care physician to be referred for TNFs treatment, he remained apprehensive and reluctant to accept that option. Due to family history of addictive disorder, Mr. S adamantly refused any opioid analgesic treatment.

Approximately 3 years earlier Mr. S was contemplating suicide and sought a psychiatric evaluation and was diagnosed with MDD for which he received treatment with the antidepressant sertraline. He responded well initially to sertraline. However, he began to experience severe frontal headaches and had to stop it abruptly. This led to the recurrence of another episode of MDD with suicidal ideation. He was then treated with the antidepressant fluoxetine. It was effective in treating the depression but caused dramatic weight gain. This side effect aggravated his AS associated pain, and the

medication was discontinued after 10 weeks. Mr. S subsequently started on citalopram, but it was stopped after 6 weeks due to the side effect of hair loss. He was then switched to the antidepressant duloxetine with its reported effects on reducing pain. However, he experienced a new onset of visual hallucination where he saw small hideous bugs flying around his food. The duloxetine was discontinued, and he began treatment with venlafaxine. Mr. S was started on 37.5 mg per day and gradually increased to 150mg per day over a period of 2 months. He was able to achieve remission with his depression while tolerated venlafaxine well without any reported adverse effects.

During a regular follow-up appointment with his primary care physician, Mr. S remarked that he has been experiencing a noticeable decrease in the degree and intensity of his AS associated neck, back and hips joint pains. He attributed the pain relief to the venlafaxine. He expressed his sincere wish to be maintained on 150mg daily dose of venlafaxine indefinitely despite the absence of any symptoms of depression. At the time of writing this report, Mr. S was contemplating on the possibility of seeking a part time employment with clerical duty from his previous construction company. His hope was to eventually get off social security disability. He also began venturing on shopping and cooking his own meals.

Discussion

Mr. S was receiving ongoing treatment of AS with the combination of celecoxib and periodic injection of GC. The combination of these medications decreased stiffness and prevented further deterioration in his spine mobility. However, he continued to suffer from neck, back and hip joint pains. The severity of these pains affects his employability and lead to his permanent disability. He was prescribed venlafaxine for the treatment of MDD, and then realized that this medication relieved him from his chronic disabling AS associated pains. Although this could be just an incidental outcome or secondary to venlafaxine effects on the remission of the MDD. Several studies have documented the effects of antidepressants on pain relief. The tricyclic antidepressants (TCAs), such as amitriptyline, doxepin, and imipramine, the serotonin norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine and duloxetine, and the atypical antidepressants, such as mirtazapine and bupropion, have been used in treating pain, especially neuropathic pain. The selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, sertraline paroxetine and citalopram, have either been less effective or have not been documented, to help with pain. While TCAs can be effective in the general management of pain, especially neuropathic pain and headache associated pain, they have been associated with burdensome adverse effects which deter patients and providers from routinely prescribing them. The most problematic TCAs side effects include weight gain, anticholinergic effects, orthostatic hypotension, cardiovascular effects, lethality in accidental or intentional overdose [28]. Compared with TCAs, the SSRIs have a milder side effects profile. However, they have shown to be either inconsistent or less effective in pain management [29]. Additionally, their potential for precipitating sexual side effects and the possibility of developing discontinuation and interruption symptoms, are considered an obstacle for their use in pain management [29]. Although the atypical antidepressant bupropion effects on decreasing pain intensity is not fully understood, it has been used in some patient with chronic pain. It is contraindicated in patients with seizures and those with eating disorders [29]. Some patients treated with bupropion may also experience excessive activation, which could paradoxically worsen their pain [29]. The antidepressant trazodone was also found to reduce pain associated with migraine headaches and diabetic neuropathy [30]. Another antidepressant mirtazapine has shown some beneficial effects in the relief of fibromyalgia associated pain and in tension headaches [31,32]. The SNRIs, duloxetine and venlafaxine, have been explored as potential beneficial agents for pain management. Duloxetine is the only antidepressant approved by the US Food and Drug Administration (FDA) for the treatment of neuropathic pain associated with diabetic peripheral neuropathy fibromyalgia, and chronic musculoskeletal pain. It has not been approved or used for the management of AS associated pain [33]. Its side effects may include nausea, somnolence, dizziness, and fatigue. The specific cause of the duloxetine-induced visual hallucinations experienced by Mr. S is unclear [34]. Venlafaxine is a mixed-action antidepressant that predominantly inhibits serotonin reuptake at low doses and norepinephrine reuptake at higher doses. Therefore, unlike the SSRIs but similar the TCAs, venlafaxine affects both key neurotransmitters that have been proposed to be involved in neuropathic pain. Venlafaxine has been shown to be effective for the management of neuropathic pain at the daily dose of 150 mg or higher, which is equivalent to the dose average used for the treatment of MDD [35]. Venlafaxine dosing guidelines including the extended release (XR) and immediate release (IR) formula and are summarized in table 2 [36]. Although venlafaxine has a milder adverse effect profile compared to the TCAs, it could precipitate hypertension and has been associated with the interruption discontinuation syndrome when abruptly discontinued [37]. Venlafaxine is FDA approved for the treatment of generalized anxiety disorder (GAD), major depressive disorder (MDD), panic disorder, with or without agoraphobia, social anxiety disorder, also known as social phobia. Its off-label use includes episodic migraine prevention; narcolepsy with cataplexy; neuropathic pain associated with diabetes mellitus; obsessive-compulsive disorder; posttraumatic stress disorder; premenstrual dysphoric disorder; and Vasomotor symptoms associated with menopause. To date there has not been any RTCs to confirm venlafaxine effectiveness as an optional treatment intervention for pain management in AS. Mr. S response to venlafaxine could be just an incidental finding or just a manifestation of its effect on the remission of the MDD. He insisted on maintaining his current daily 150mg dose due to its dramatic effects on pain relief and overall improvement of daily functioning. He consented to accept its off-label use for the management of his AS associated chronic disabling pain. He agreed and contracted to promptly report any emergence of venlafaxine induced side effects including any acute emergence of suicidal ideation.

Table 2: Venlafaxine Dosing Guidelines

Usual dosage range : 75-225 mg/day (can be dosed higher) • XR: once daily • IR: divided into 2-3 doses Dosage forms • Capsule (XR): 34.5 mg, 75 mg, 150 mg • Tablet: 37.5 mg, 75 mg, 150 mg, 225 mg • Scored tablets: 25 mg, 37.5 mg, 75 mg, 100 mg

Conclusion

The evidence from RCTs seems to indicate that venlafaxine is beneficial in the management of neuropathic pain, its clinical relevance on the relief of the chronic disabling pain associated with AS is uncertain. More rigorous RTCs are needed to confirm the effectiveness of venlafaxine as an evidence-based treatment for the management of AS associated pain.

Conflict of Interest Statement

The authors reports no conflict of interest. The patient identifying characteristics have been changed to protect the confidentiality of the medical records and the integrity of clinical practices.

The materials described in this manuscript are those of the authors and do not reflect the views of the Department of Veterans Affairs or the VA Central California Health Care System or the Department of Psychiatry of UCSF -Fresno medical Education Program or Fresno County Department of Behavioral Health.

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