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Off-label use of duloxetine for pediatric neuropathic pain

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Abstract

Introduction: Duloxetine, a serotonin-norepinephrine reuptake inhibitor, has been used successfully for adults for the management of neuropathic pain syndromes. Pediatric data are needed because inadequate neuropathic pain management in children and adolescents results in lower psychosocial functioning, delayed development, and decreased quality of life. We aim to describe a case series on the use of duloxetine for the management of symptoms associated with chronic neuropathic pain syndromes in a pediatric population.

Methods: Data were collected in a naturalistic, consecutive, case report format, from a pediatric pain management clinic for children prescribed duloxetine for analgesia for a variety of neuropathic-type pain conditions. Follow-up data, including self-report of pain, and type and frequency of adverse reactions, were collected to describe the efficacy and safety of duloxetine.

Results: Duloxetine was prescribed for the management of self-reported average pain scores of greater than 5 out of 10 on the Faces Pain Scale–Revised for pain that was resistant to other medications. Each of these patients had comorbid psychiatric diagnoses. Reduction in pain following duloxetine therapy was not universal, and all patients discontinued duloxetine therapy prematurely because of adverse effects.

Conclusion: Further evidence is needed to demonstrate the efficacy and safety of duloxetine for use in pediatric populations with neuropathic components to their pain. Based on our experience, we suggest considering its use only after failure of other agents. The best management of a pediatric patient's pain condition is likely accomplished through a combination of pharmacotherapy and nonpharmacotherapy interventions.

Keywords: duloxetine, pediatric, neuropathic, pain

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Introduction

Neuropathic pain involves damage to neural tissues and can develop from a variety of conditions, such as fibromyalgia, headache syndromes, complex regional pain syndrome, orofacial pain, and neuralgias.[1,2] Neuropathic pain is less common in childhood, and epidemiologic studies have not been conducted to characterize its true prevalence; however, juvenile primary fibromyalgia syndrome may account for 25% to 40% of pediatric chronic pain syndromes.[3] Additionally, neuropathic pain and complex regional pain syndrome may account for up to 40% of referrals to pediatric pain clinics.[4,5] Research has also demonstrated the interplay of chronic pain and psychiatric disorders. Anxiety and depression are two common psychiatric problems in pediatric patients with chronic pain.[6] The underlying mechanism of neuropathic

pain syndromes in children and adolescents is not fully known; however, injury from competitive sports, dance, trauma, and cancer are known risk factors for the development of neuropathic pain. The presentation of neuropathic pain may differ between adults and children; however, common symptoms can include burning, tingling, and allodynia.[7] For a further in-depth discussion of pain syndromes in the pediatric pain population, please refer to the review by Walker.[8]

The management of neuropathic pain for children is largely based on adult treatment guidelines. There is a paucity of well-designed, randomized, controlled studies and Food and Drug Administration (FDA)–approved medications for all pediatric age groups. Children and adolescents often present with rare conditions that differ from adult patients regarding level of acuity, presentation, and comorbid states.[9] Therefore, extrapolation of adult data may not appropriately fit the pediatric population. These gaps in knowledge often lead to delayed diagnosis and inadequate evaluation.[10] Suboptimal treatment of pediatric pain syndromes can have substantial implications for the treatment of psychiatric disorders.[11-13] Children with chronic pain commonly experience delayed psychosocial development, loss of physical function, absence from school, and increased visits to the emergency department and pain clinic. Thus, there is a need to critically evaluate the management of neuropathic pain for these vulnerable patients.

A multimodal treatment approach that combines medications with synergistic mechanisms of action is needed to address the unique aspects of neuropathic pain. Several adjuvant analgesics have been used effectively in adult patients, including tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors, and anticonvulsants. Opioids are not preferred for long-term management of these conditions because neuropathic symptoms generally respond poorly to this class of medication. Patients and parents frequently discontinue opioids secondary to side effects of sedation, dependence, abuse risk, and exacerbation of certain types of neuropathic pain.[14]

The tricyclic antidepressants have a longer history of use in pediatric pain management but are limited by their histaminergic, adrenergic, and cholinergic side effects.[15] The dose response range for tricyclic antidepressants in neuropathic pain is wide, and it may take several weeks to titrate to analgesic effect. Experience with SSRIs has been limited in pediatric analgesia.[16-18] Serotonin-norepinephrine reuptake inhibitors may have advantages in pain syndromes over SSRIs because of the added inhibition of norepinephrine reuptake. Noradrenergic models, and to a lesser extent serotonergic models, have been shown to reduce painlike behavior in preclinical populations.[19] The serotonin-norepinephrine reuptake inhibitor duloxetine has been used successfully for managing neuropathic pain syndromes, including fibromyalgia, in adult patients.[20,21] To date, no trials have demonstrated the efficacy of duloxetine in childhood neuropathic pain.

Currently, there are 3 case reports published on the safe and effective use of off-label duloxetine in children and adolescents ages 10 to 17 years for the management of chronic neuropathic pain.[22-24] These reports document a total of 4 pediatric patients with varying comorbid disease states where pain was successfully controlled with duloxetine. We aim to describe the use and outcomes of duloxetine in a pediatric population through a series of cases seen in our clinic.

Methods

Here, we report our experience initiating duloxetine for the management of neuropathic pain in 5 consecutive pediatric patients treated in the multidisciplinary pain clinic at the Children's Hospital of Michigan in the Detroit Medical Center during a 6-month period in 2013 (Table 1). Although exact conditions varied across our patient cases, each patient had a neuropathic component to his or her chronic pain condition. Demographic data, etiology of pain symptoms, clinical presentation, causes of symptoms, prior treatments, pain response (Faces Pain Scale-Revised [FPS-R]), medication changes, and adverse effects were documented before and after exposure to duloxetine, which is standard for patient documentation in our clinic. Data, including changes in pain scores (FPS-R), were collected for each patient at baseline and at 6- and 12-week follow-up visits.

Results

Case 1

A 14-year-old African American female was referred to the pain clinic because of uncontrolled diffuse pain in the lower back and spine area. The patient stated that she had been having overall body pain for the past 2 years that began at the time she received a diagnosis of juvenile rheumatoid arthritis, which was managed primarily with naproxen. Past medical history was also significant for Major Depressive Disorder, scoliosis, and a possible diagnosis of fibromyalgia.

During the past year, the patient identified worsening pain. Most of the pain was in her back and spine, although she also had pain in her legs that radiated throughout her body. At baseline, she rated her pain as 8 out of 10 (with 10 being the worst). She described disturbed sleep due to the pain. She missed approximately 15 days of school in

TABLE 1: Patients treated with duloxetine for neuropathic pain conditions

Case No.	1	2	3	4	5
Age, y	14	16	13	16	17
Sex	F	F	M	F	F
Weight, kg	41.5	66.1	65.2	50.2	108.5
Height, cm	138.9	142.7	163.2	168.5	147.4
Primary pain condition	FM	CRPS	Left leg pain	Diffuse pain–all extremities	Headache Eye pain
Secondary pain condition	JRA	Hip bursitis	CRPS	n/a	Spasms
Comorbid conditions	Dextroscoliosis Depression	Gastric reflux Depression Insomnia	Depression Insomnia	Diabetes mellitus type 1 Neuropathy Insomnia Depression	Epilepsy PTSD Depression
Duloxetine regimen	30 mg every morning with food	30 mg every morning, then 20 mg every evening at week 6 with food	Titrated to 90 mg daily Changed to 60 mg daily with food	30 mg every morning with breakfast	60 mg every morning with breakfast
Other analgesics/ medications	Naproxen Polyethylene glycol 3350 Omeprazole Failed: amitriptyline, ranitidine, gabapentin	Ranitidine Naproxen Melatonin Failed: ibuprofen	Clonazepam Failed: tramadol, tizanidine, trazodone, pregabalin	Gabapentin Enalapril Insulin Ibuprofen Diazepam Failed: amitriptyline	Hydrocodone/ acetaminophen Ibuprofen Baclofen Clonazepam Lamotrigine Failed: escitalopram, pregabalin, topiramate, amitriptyline
Duration of primary pain	2 y	4 y	5 y	6 mo	5 y
Pain score at baseline visit	8-10	8	6	8	5
Pain score at 6 wk	8-10	5-6	6	7	6
Pain score at 12 wk	NA[a]	NA[a]	6	7	6
Adverse effects–duloxetine	Rash/nausea	Nausea	Nausea	Chest pain/nausea	Nausea
Reason for duloxetine discontinuation	Adverse effects	Adverse effects	Adverse effects	Adverse effects Lack of efficacy	Adverse effects Lack of efficacy

CRPS = chronic regional pain syndrome; FM = fibromyalgia; JRA = juvenile rheumatoid arthritis; n/a = not applicable; PTSD = posttraumatic stress disorder.

[a]Pain scored as "NA" if duloxetine was discontinued.

the past 6 months, which had a negative impact on her grades.

The patient had an adequate trial of physical therapy with no benefit. The pain failed to respond to trials of naproxen, gabapentin, and amitriptyline. She was started on 30 mg of duloxetine by mouth every morning. Six weeks after starting duloxetine, the patient reported consistent nausea and a rash that encompassed her arms, face, upper back, and some spots on her legs. She reported no change in her pain score, and duloxetine was discontinued. The nausea and rash resolved and her pain remained unchanged.

Case 2

A 16-year-old white female presented to the pain clinic with complex regional pain syndrome that originated unprovoked from her abdominal area and progressed over "years" to generalized pain in the bones. The patient attempted to alleviate the pain by limiting physical activity and taking ibuprofen 600 mg by mouth 3 times

a day, with inadequate relief. Past medical history was significant for acid reflux, Major Depressive Disorder, and insomnia.

At baseline, the patient described her pain as 8 out of 10. She stated that she is usually very active and enjoyed going to physical therapy once a week in hopes of returning to her prior level of functioning. The pain interfered with her academic performance to the point where she dropped out of school to be homeschooled. She was started on duloxetine 30 mg every morning. Six weeks later, she reported pain scores of 5 to 6 out of 10; however, nausea was a significant side effect. An attempt was made during approximately 2 weeks to lower the dosage of duloxetine to 20 mg daily and change the time of dose administration to the evening. Nausea persisted despite these interventions, and duloxetine was then discontinued during week 8 of therapy. Within 3 weeks of discontinuation, her nausea completely resolved.

Case 3

A 13-year-old white male presented with uncontrolled localized pain originating in the right upper thigh and radiating down to the calf muscle secondary to thigh cellulitis caused by a spider bite 2 years prior. Past medical history included insomnia and Major Depressive Disorder. He was homeschooled, yet he was social with his core group of friends. Pain was rated as 6 out of 10. Conversion disorder was ruled out by his community psychiatrist, and it was decided that his pain syndrome was predominately sympathetic in nature. In consultation with his community psychiatrist (not associated with our clinic), duloxetine was titrated to 90 mg daily during 6 weeks. At his 6-week follow-up, the patient said he had been nauseated daily and reported little relief of pain. Duloxetine was subsequently lowered to 60 mg because of nausea. At his 12-week follow-up, his nausea was still present, with no improvement in pain, so duloxetine was tapered over an unknown number of weeks by his community psychiatrist and discontinued. His nausea resolved.

Case 4

A 16-year-old white female presented with diffuse tingling and numbness in her hands and feet that began 6 months prior. Her past medical history was significant for type 1 diabetes mellitus, neuropathy, hypertension, and depression.

At baseline, the patient stated she had a hard time sleeping because of pain (8 out of 10) and could only attend school for a half a day because of drowsiness secondary to gabapentin. Patient was recounseled on the importance of glucose control because this may contribute to her neuropathic symptoms. Blood glucose monitoring results were unavailable. Amitriptyline was discontinued, and she was started on duloxetine 30 mg every morning and diazepam 10 mg by mouth as needed for sleep. At 6 weeks, the patient reported a "small" reduction in pain, decreased to 7 out of 10, so therapy was continued. Approximately 12 weeks later it was noted that the patient went to the emergency room 3 months after her first clinic visit because of chest wall pain and nausea. Patient rated her pain as unchanged, 7 out of 10 and duloxetine was discontinued. The patient had no further episodes of chest pain or nausea.

Case 5

A 17-year-old white female was referred to the pain clinic because of uncontrolled pain behind her right eye and around the area of a craniotomy. The craniotomy was performed 5 years earlier because of a motor vehicle accident and traumatic brain injury. In addition to the pain following the traumatic brain injury, patient had epilepsy that was controlled with lamotrigine 100 mg by mouth 3 times a day.

At baseline, the patient rated her pain as 5 out of 10. Past medical therapies had included supraoccipital injections, escitalopram, topiramate, amitriptyline, and pregabalin (doses unknown), with little relief. The patient reported minimal relief with hydrocodone-acetaminophen 5/500 mg by mouth once daily, baclofen 40 mg by mouth 3 times daily, and ibuprofen 600 mg by mouth 3 times daily as needed. Duloxetine was initiated at 30 mg every morning and titrated to 60 mg every morning during a 3-week period.

At 6 weeks, the patient rated her pain as 6 out of 10 with occasional nausea; however, she related an increase in confidence and mood secondary to being able to play basketball again. Given the perceived benefit on her mood symptoms, duloxetine was continued in order to assess for added benefit in the treatment of pain. At 12 weeks, the patient still complained of severe headaches with intermittent nausea. The patient stated she strongly believed nausea was related to duloxetine and she decided to discontinue duloxetine. Nausea fully resolved after discontinuation.

Discussion

We have described the off-label use of duloxetine for neuropathic pain in an adolescent population. Each case resulted in discontinuation of duloxetine because of either adverse effects, lack of efficacy, or both. The primary adverse effect of nausea was not improved with altered administration times or coadministration with food, yet resolved after discontinuation of duloxetine. To date, only

TABLE 2: Previous reports of duloxetine for pediatric neuropathic pain

Source, y	Desarkar et al,[23] 2006	Meighen,[24] 2007	Kachko et al,[22] 2011
Study design	Case report	Case series	Case report
Sample size	1	2	1
Female, %	100	100	100
Age, y	10	14, 16	16
Pain condition(s)	Diffuse in right part of chest and right leg	Case 1: lower back and hip; case 2: abdominal	Lower right extremity following electrophysiology study and ablation procedure
Comorbid condition(s)	MDD with psychosis and dissociative symptoms	Case 1: MDD and pain disorder associated with psychologic symptoms; mild mitral valve prolapse; case 2 Crohn disease; MDD	Mood disorder due to general medical condition ("reactive depression"), insomnia, obesity
Duloxetine daily dose	20 mg titrated to 60 mg daily	Case 1: 20 mg titrated to 40 mg daily; case 2: 20 mg titrated to 40 mg daily	20 mg titrated to 60 mg daily
Adverse effects	None	None	None
Overall result	Resolution of depressive and psychotic symptoms (also on olanzapine 15 mg/d) within 3 wk. Continued improvement at 3-mo follow-up. Actual pain scores not reported.	Case 1: decrease of pain from 10/10 to 0/10 and euthymic at 4-mo follow-up; case 2: decrease of pain from 9/10 to 0/10 and euthymic at 3.5-mo follow-up	At 6-mo follow-up, pain decreased from 9/10 to 0/10 to 1/10 and euthymic

MDD = Major Depressive Disorder.

3 reports exist describing cases of duloxetine use for pediatric pain.[7-9] Briefly, a case series by Meighen[24] reported the successful use of duloxetine in adolescent females with comorbid chronic pain and depression. A second report by Desarkar et al[23] described the successful use of duloxetine for a pediatric patient with depression, severe pain, and dissociative symptoms. The third case, by Kachko et al,[22] reported the successful use of duloxetine in a female pediatric patient with femoral neuropathy and "reactive depression" with conversion symptoms. Although each report described the successful use of duloxetine (summarized in Table 2), to date there have been no prospective trials looking at the efficacy of duloxetine for pediatric neuropathic pain management. Although our case series reports a lack of efficacy and side effects with duloxetine's use, our population is different from each of the other case reports, making comparisons difficult. Clinicians must bear in mind that a modest decrease in pain score may appear insignificant; however, for a neuropathic pain condition, a decrease of 30% may indicate clinical effectiveness.[25]

Overall, nausea is the most common side effect of duloxetine therapy compared with placebo.[26-28] The mechanism of duloxetine-induced nausea is not completely understood but may be related to its mechanism of action at the serotonin and norepinephrine receptors. Nausea is also a common side effect of the other SSRIs; however, it may be more common in duloxetine compared with other SSRIs.[27] Compared with adults treated with venlafaxine, nausea is reported more frequently by adolescents.[29-31]

Many potential barriers to pediatric medication adherence have been identified, and furthermore, adherence has been linked to health outcomes in this population.[32-34] Thus, potentially troubling side effects, like nausea, can substantially inhibit the efficacy of promising agents, like duloxetine, for neuropathic pain. Additionally, duloxetine, like all antidepressants, carries an FDA boxed warning about increased suicidal thinking and behavior for children, adolescents, and young adults, which can increase both patient and parental anxiety regarding medication use. Self-monitoring plans enhance the effectiveness of pain therapy and minimize the risk of serious side effects, such as increased suicidal thoughts and behaviors.[26]

Finally, duloxetine is now available in a generic formulation, which aids in affordability. Because it is a moderate inhibitor of cytochrome P450 2D6, it has the potential for drug-drug interactions; therefore, adequate examination of the patient's medication profile during drug therapy changes is necessary.

Conclusion

Off-label use of duloxetine continues to be an option for relief of neuropathic pain syndromes in adolescents despite the lack of prospective evidence. Because chronic pain often occurs with depression (present in every case report to date), it can be difficult to fully elucidate the underlying etiology of the disorders because they are interrelated and likely interdependent. Thus, serotonin-norepinephrine reuptake inhibitors are attractive options to address both depressive and pain symptoms with a single medication; however, it is essential that appropriate monitoring and precautions be taken prior to prescribing duloxetine. Monitoring and screening must be initiated before prescribing this agent to this vulnerable population because the risks can outweigh the benefits. Education on side effects and the importance of adherence is key, especially for adolescents. Based on our experience of using duloxetine in a pediatric population with neuropathic components to their pain, we suggest considering its use only after failure of other agents. We believe that pharmacotherapeutic options, such as gabapentin, tricyclic antidepressants, or transdermal lidocaine, may be more appropriate, depending on patient-specific factors. If these options fail, we then would consider a trial of duloxetine after considerable patient education and careful, slow titration of the drug. Overall, the best management, in our opinion, of a pediatric patient's pain condition is likely accomplished through a combination of pharmacotherapy and nonpharmacotherapy interventions.

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