CASE REPORT

Duloxetine contributing to a successful multimodal treatment program for peripheral femoral neuropathy and comorbid 'reactive depression' in an adolescent

Ludmyla Kachko MD[1,2], Shiri Ben Ami BPT[1,3], Alon Liberman MA[1,4], Einat Birk MD[5], Sefi Kronenberg MD PhD[4,6]

L Kachko, S Ben Ami, A Liberman, E Birk, S Kronenberg. Duloxetine contributing to a successful multimodal treatment program for peripheral femoral neuropathy and comorbid 'reactive depression' in an adolescent. Pain Res Manage 2011;16(6):457-459.

In the United States, duloxetine has been approved for the treatment of major depressive disorder, diabetic peripheral neuropathic pain and fibromyalgia in the adult population. Data regarding the use of duloxetine in the pediatric population, however, are very limited. Femoral nerve injury is a rare complication of cardiac catheterization. In the case described, duloxetine contributed to a successful multimodal treatment program for peripheral neuropathic pain due to femoral neuropathy in an adolescent with 'reactive depression' and conversion symptoms. To the best of the authors' knowledge, the present article is only the third such report on this dual use of duloxetine in children and adolescents, and the first report of such treatment following femoral neuropathy induced by cardiac catheterization.

Key Words: *Adolescent; Depression; Duloxetine; Femoral neuropathy*

L'apport de la duloxétine à la réussite d'un programme thérapeutique multimodal de la neuropathie fémorale périphérique et d'une « dépression réactive » comorbide chez un adolescent

Aux États-Unis, la duloxétine est approuvée pour le traitement des troubles dépressifs majeurs, de la douleur neuropathique périphérique du diabèteet de la fibromyalgie au sein de la population adulte. Les données relatives à l'utilisation de la duloxétine au sein de la population pédiatrique sont toutefois limitées. Le traumatisme du nerf fémoral est une rare complication du cathétérisme cardiaque. Dans le cas décrit, la duloxétine a contribué à la réussite d'un programme thérapeutique multimodal de la douleur neuropathique périphérique causée par une neuropathie fémorale chez un adolescent ayant une « dépression réactive » et des symptômes de conversion. En autant que le sachent les auteurs, le présent article est seulement le troisième rapport de cette double utilisation de la duloxétine chez les enfants et les adolescents, et le premier rapport d'un tel traitement après une neuropathie fémorale induite par un cathétérisme cardiaque.

Treatment of children and adolescents with chronic pain and comorbid depression is challenging due to the lack of treatment protocols. Duloxetine is a dual reuptake inhibitor of serotonin and norepinephrine, which has been approved for the treatment of major depressive disorder (MDD), diabetic peripheral neuropathic pain and fibromyalgia in the adult population (1-3). Data regarding the use of duloxetine in children and adolescents are very limited. In the case described, duloxetine contributed to a successful multimodal treatment program for peripheral neuropathic pain in an adolescent with 'reactive depression' (The term 'reactive depression' is a common clinical diagnosis, meaning a depression that was induced by a specific cause. However, the proper term for such a depression in the DSM-IV-TR is mood disorder due to a general medical condition) and conversion symptoms. The current literature is briefly reviewed to discuss the indications for duloxetine in such patients.

CASE PRESENTATION

A 16-year-old female adolescent of Jewish Ashkenazi descent (height 163 cm, weight 87 kg) from an orthodox religious family, was admitted to a pediatric chronic pain clinic at a tertiary children's hospital due to chronic pain in her right lower extremity. Six months before the admission, she was diagnosed with Wolf-Parkinson-White (WPW) syndrome with supraventricular tachycardia (SVT) and, six weeks before her admission, she underwent an electrophysiology study (EPS) and ablation procedure under general anesthesia.

For the EPS, right femoral artery and vein cannulations were performed. From the time she was diagnosed with WPW and scheduled for EPS, she experienced depressed mood, had difficulty with concentration and was very nervous and frightened about the upcoming procedure.

There were no previous episodes of either depression or anxiety and, on a psychiatric evaluation with a private adult psychiatrist four months before admission to the pain clinic, she was diagnosed with reactive depression due to a general medical condition. No written documentation was provided by the family, but according to the parents report, treatment with the selective serotonin reuptake inhibitor fluoxetine at 20 mg/day was prescribed. The patient, however, did not receive the medication on a regular basis.

Two days after the EPS procedure, she began complaining of severe pain in her right lower extremity. Physical examination by a pediatric cardiologist revealed no hematoma or swelling at the puncture site, and symptomatic treatment with nonsteroidal anti-inflammatory drugs was initiated without effect. Subsequently, her underlying SVT recurred; she was admitted several times to the emergency department and was scheduled for a second EPS and ablation. Pharmacological treatment of the recurrent SVT was commenced with atenolol (a cardioselective beta-adrenergic blocker).

Three weeks after the initial EPS procedure (and three weeks before admission to the pain clinic), the patient complained of headaches, mild jerking of arms and sudden reversible loss of vision for several seconds and was hospitalized in an internal pediatric department for investigation. Electroencephalogram and magnetic resonance imaging of the brain revealed no pathology. Blood analysis and electrolyte levels were within normal limits. A urine pregnancy test

[1]*Chronic Pain Clinic, Pain Treatment Service;* [2]*Department of Anesthesia;* [3]*Physiotherapy Unit;* [4]*Department of Psychological Medicine;* [5]*Pediatric Heart Institute;* [6]*Feinberg Child Study Center; Schneider Children's Medical Center of Israel, Petah Tiqwa; Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*

Correspondence: Dr Ludmyla Kachko, Department of Anesthesia, Schneider Children's Medical Center of Israel, 14 Kaplan Street, Petah Tiqwa 49202, Israel. Telephone 972-3-925-30-80 fax 972-3-925-32-79, e-mail kachko_l@hotmail.com

was negative. Consultation was sought with the in-house pediatric psychiatry service within 48 h of the patient's admission. Her affect was depressed and she described her mood as "sad and angry about herself". Self-directed anger is a common feature of pediatric depression (4). She reported increased sleepiness and fatigue that had developed over a period of one month.

The parents pointed out that the above-mentioned symptoms (headaches, mild jerking of arms and sudden reversible loss of vision) were apparent periodically ever since the patient received the diagnosis of WPW, but the family opted not to investigate further. The girl was given a DSM-IV-TR diagnosis of mood disorder due to her general medical condition and conversion disorder (conversion symptoms appeared after the onset of depression).

Treatment with fluoxetine 20 mg/day was reinitiated. After one week of treatment in the internal pediatric department, the patient was discharged with recommendation for physiotherapy treatment (PT) at the rehabilitation unit and was consequently referred to the pediatric chronic pain clinic.

At the time of her primary evaluation, the patient made no eye contact and refused to speak. On a firm request by her father to communicate with the staff, she complained of severe burning pain in the right groin and the anterior aspect of the thigh radiating down the medial aspect of the leg up to the big toe. She pointed to an 8-9/10 on a visual analogue scale (VAS). The pain was aggravated during physical effort, and for ambulation she used forceful external rotation of the extremity to compensate for not putting weight on her heel. Neurological examination revealed weakness of the right quadriceps muscle, decreased patellar reflex, allodynia and paresthesia along the distribution of the saphenous nerve. She was able to pull, but not straighten, her right leg because of quadriceps muscle weakness. Patchy sensory anesthesia over the anterior and medial parts of the thigh was also present. The remainder of the neurological examination was normal. At that time, her medications consisted of atenolol 25 mg twice daily, amitriptyline 25 mg once daily, carbamazepine 200 mg twice daily and fluoxetine 20 mg once daily. Treatment with amitriptyline and carbamazepine was started by the family physician after her discharge form the internal pediatric department, exactly one week before the admission to the pain clinic.

The patient reported being sad over her physical condition, and was now angry with the hospital medical personnel and refused to participate in PT. Despite her depressed mood, the family continued to refuse a consultation by an in-house child and adolescent psychiatrist or psychologist. They also refused a consultation by the previously mentioned private adult psychiatrist. The parents expressed fear that by seeking psychiatric/psychological therapy, they might ruin their daughter's chances of finding a suitable match for marriage, which is usually arranged after careful investigation. Subsequent to a thorough explanation, the parents agreed for the patient to be evaluated by the chronic pain clinic psychologist, and standard clinical psychological intake and anamnesis were obtained. No psychotic symptoms, passive wishes to die or suicidal intent were noted. The adolescent was diagnosed as suffering from right femoral neuropathy and 'reactive depression' with conversion symptoms and *la belle indifference* (being mute for most of the day and indifferent to that situation).

A combined treatment with duloxetine, femoral nerve blocks and PT was proposed. Duloxetine was chosen because higher dosages of amitriptyline were considered to be too risky for a patient with a diagnosis of WPW, and carbamazepine possesses very little antidepressive properties. However, before making final decision, the parents opted for a single consultation with a private child and adolescent psychiatrist and to discuss matters with a family Rabbi. The family said it would take two weeks for both meetings to transpire. Because the adolescent refused to engage in PT at that time, at either the hospital or in a community setting, or receive femoral nerve blocks, her ankle was temporarily immobilized to prevent Achilles tendon shortening. The parents and the patient received a letter from the chronic pain clinic team (a senior specialist in pediatric pain, psychologist and PT specialist) with the diagnosis and recommendations for further investigation (electromyography of the lower extremities and ultrasonographic examination of the right groin) and the above-mentioned proposed treatment.

Electromyography of the lower extremities revealed signs of right femoral neuropathy, and no hematoma or pseudoaneurysm was found on ultrasonographic examination of the right groin. Two weeks later, after consultation with the private psychiatrist and family Rabbi, informed consent for the proposed treatment was obtained from the parents and assent was obtained from the patient. Carbamazepine was discontinued and amitriptyline was cross tapered (discontinued over five days) with duloxetine at a dose of 20 mg/day. After one week of treatment with duloxetine, the patient agreed to participate in PT sessions (2 h sessions; four times a week), but continued to experience pain in the right leg (VAS 7-8/10). She denied any adverse effects of duloxetine, and the dose was gradually increased to 60 mg/day. Ultrasound-guided femoral blocks with bupivacaine 0.5% and methylprednisolone 10 mg (synthetic glucocorticoid drug; Solu-Medrol [Pfizer, Belgium]) (n=6) were performed once a week to increase her active participation in PT. Her leg pain had gradually decreased (VAS 2-3/10) and, after one month of PT treatment at the rehabilitation unit, she continued her PT at home.

Three months after starting treatment, the patient was scheduled for EPS and ablation for her recurrent WPW with SVT at another hospital. The pain clinic staff advised the cardiologist not to use the right femoral vessels for the cannulation (if possible), and the procedure was successfully performed through the left approach.

Six months after starting treatment, the patient rated her pain typically at 0-1/10 and was continued on duloxetine 60 mg/day at night without any side effects. Her mood improved considerably and she returned to her regular activities. At that time, the family began their search for an appropriate match for marriage. After final evaluation by the chronic pain clinic staff, duloxetine was tapered-off over two weeks. After her marriage, the patient was lost to follow-up.

DISCUSSION

Pain conditions in children and adolescents have a substantial impact on psychosocial functioning. In a study by Kashikar-Zuck et al (5), most of the pediatric patients with chronic pain conditions demonstrated mild to moderate levels of depression, and approximately 15% reported severe levels of depression. Notwithstanding, there may be an independent association between depression and pain. The diagnosis of painful symptoms as a part, or not, of a depressive disorder requires appropriate physical and laboratory examinations and specialist referral (6).

Femoral nerve injury is a very rare complication of cardiac catheterization, with a reported incidence of 0.21% (7). It is usually caused by direct trauma during femoral vessel access, compression from a hematoma or prolonged digital pressure for postprocedural hemostasis (7,8). Direct trauma and/or pressure applied to the puncture site for hemostasis were the implicated causes in the present case. The adolescent was obese, and vessel cannulation was reported to be difficult. When the procedure is performed on an awake patient, he or she may feel paresthesia when the tip of the needle contacts the femoral nerve (9). In our case, the procedure was performed under general anesthesia (as usual with children and adolescents) and the immediate diagnosis of direct trauma was not established. The patient's femoral nerve injury was the first to occur in our pediatric catheterization laboratory in 18 years, in which more than 400 catheterizations are performed yearly. Moreover, our patient suffered from depression with conversion symptoms and *la belle indifference*, which led to a breakdown in communication and further delay with the diagnosis and treatment.

Treatment options for femoral neuropathy include early recognition and correction of any reversible etiology. An aggressive PT

program is recommended early in the course of the neuropathy to decrease the risk of muscle wasting and contractures (10,11). Kuntzer et al (12) concluded that irrespective of the cause of femoral mononeuropathy, functional improvement could be achieved in two of three patients within two years of onset. In the case described, the treatment dilemma consisted of an association between femoral neuropathy and 'reactive depression' with conversion symptoms in a patient from an orthodox Jewish family that refused PT.

There is a long history of mistrust and opposition to the use of psychiatry and psychotherapy among the strictly orthodox Jewish community. Perhaps the most important issue in serving Orthodox Jews is to treat clients with respect and sensitivity to individual and family beliefs and preferences, and to obtain recommendation from a family Rabbi (13,14). Interestingly, many Orthodox Jews prefer psychopharmacotherapy over psychotherapy (15). Considering all above-mentioned problems, we considered duloxetine to be the optimal drug of choice for our patient.

Duloxetine, a serotonin norepinephrine reuptake inhibitor, was initially used in the treatment of MDD alone or in association with chronic pain (6). Recently, duloxetine has been included in guidelines written by the International Association for the Study of Pain, a special interest group for the pharmacological treatment of neuropathic pain (16). The United States Food and Drug Administration and the European Medicines Agency have approved its use in the treatment of diabetic peripheral neuropathic pain in adults. The Food and Drug Administration also approved its use for the management of fibromyalgia (1-3).

Reports on the usage of duloxetine in children are very limited. We searched PubMed in December 2010, and were able to find only two publications reporting the treatment of children and adolescents with duloxetine for MDD and chronic pain. Desarkar et al (17) reported on the successful use of duloxetine in a 10-year-old girl with MDD and psychotic and dissociative symptoms who also experienced severe pain. Two adolescent females with chronic pain and comorbid MDD were described by Meighen (18). To the best of our knowledge, the present report is the first to describe duloxetine use for the combined treatment of isolated peripheral neuralgia with associated depression.

A clinical question arose when duloxetine was proposed in the patient's case, a patient with underlying SVT. In general, duloxetine does not seem to be associated with significant cardiovascular changes and risks (19). However, it might have some arrhythmia effect through decreasing the R-R, QRS and QT intervals (20). Also, being a moderate inhibitor of CYP2D6, duloxetine may affect serum concentrations of several drug classes, including β-blockers, and type 1C anti-arrhythmics (21). Because our patient received the β-blocker atenolol for her recurrent SVT, a permission to use duloxetine was obtained from a cardiologist. No worsening of SVT was noted during duloxetine therapy and there was also no need for atenolol dose adjustment. Furthermore, after the successful second EPS, atenolol was discontinued. Atenolol, similar to other β-blockers, may rarely cause depression, headaches, jerking of extremities and visual disturbances, but the patient's depression and conversion symptoms began many weeks before this drug was initiated and, after initiation, there were no changes in the above-mentioned symptoms.

CONCLUSION

In the case described, duloxetine contributed to a successful multimodal treatment program for peripheral neuropathic pain due to femoral neuropathy in an adolescent with 'reactive depression' and conversion symptoms. There were no apparent complications from the treatment. The improvement in the mental state of the patient offered the opportunity to proceed with PT, which is imperative for preventing long-term disability associated with peripheral femoral neuralgia. It should be noted, however, that antidepressants have the potential to increase suicidality in the pediatric population (22), and this risk may be even more significant with off-label use, such as duloxetine for pediatric depression. Additional studies are necessary to assess the efficacy and safety of duloxetine in the treatment of pediatric mood disorders, especially in combination with chronic pain syndromes.

REFERENCES

1. Attal N, Cruccu G, Haanpää M, et al; EFNS Task Force. EFNS guidelines on pharmacological treatment of neuropathic pain. Eur J Neurol 2006;13:1153-69.
2. New drug for neuropathic pain. FDA Consumer 2004;38:2.
3. Food and Drug Administration. NDA approval letter <www.fda.gov/cder/foi/appletter/2008/022148s000ltr.pdf> (Accessed on March 1, 2009.
4. Nigg JT. Temperament and developmental psychopathology. J Child Psychol Psychiatry 2006;47:395-422.
5. Kashikar-Zuck S, Goldschneider KR, Powers SW, Vaught MH, Hershey AD. Depression and functional disability in chronic pediatric pain. Clin J Pain 2001;17:341-9.
6. Wise TN, Fishbain DA, Holder-Perkins V. Painful physical symptoms in depression: A clinical challenge. Pain Med 2007;(8 Suppl 2):S75-82.
7. Kent KC, Moscucci M, Gallagher SG, DiMattia ST, Skillman JJ. Neuropathy after cardiac catheterization: Incidence, clinical patterns and long term outcome. J Vasc Surg 1994;19:1008-13.
8. Kuruvilla A, Kuruttukulam G, Bimal F. Femoral neuropathy following cardiac catheterization for balloon mitral valvotomy. Int J Cardiol 1999; 71: 197-8.
9. Barçin C, Kursaklioglu H, Köse S, Isik E. Transient femoral nerve palsy after diagnostic coronary angiography. Anadolu Kardiyol Derg 2009;9:248-9.
10. Groah SL, Cifu DX. The rehabilitative management of the traumatic brain injury patient with associated femoral neuropathy. Arch Phys Med Rehabil 1995;76:480-3.
11. Warfel BS, Marini SG, Lachmann EA, Nagler W. Delayed femoral nerve palsy following femoral vessel catheterization. Arch Phys Med Rehabil 1993;74:1211-5.
12. Kuntzer T, van Melle G, Regli F. Clinical and prognostic features in unilateral femoral neuropathies. Muscle Nerve 1997;20:205-11.
13. Loewenthal KM. Strictly orthodox Jews and their relations with psychotherapy and psychiatry. WCPRR 2006; 1: 128-132
14. Schnall E. Multicultural counseling and the Orthodox Jew. J Counsel Dev 2006;84:276-82.
15. Greenberg, D. Is psychotherapy possible with unbelievers?: The care of the ultra-orthodox community. Isr J Psychiatry Relat Sci 1992;28:19-30.
16. Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: Evidence-based recommendations. Pain 2007;132:237-51.
17. Desarkar P, Das A, Sinha VK. Duloxetine for childhood depression with pain and dissociative symptoms. Eur Child Adolesc Psychiatry 2006;15:496-9.
18. Meighen KG. Duloxetine treatment of pediatric chronic pain and co-morbid major depressive disorder. J Child Adolesc Psychopharmacol 2007;17:121-7.
19. Thase ME, Tran PV, Wiltse C, Pangallo BA, Mallinckrodt C, Detke MJ. Cardiovascular profile of duloxetine, a dual reuptake inhibitor of serotonin and norepinephrine. J Clin Psychopharmacol 2005;25:132-40.
20. Wernicke J, Lledo A, Raskin J, Kajdasz DK, Wang F. An evaluation of the cardiovascular safety profile of duloxetine: Findings from 42 placebo-controlled studies. Drug Saf 2007;30:437-55.
21. Janicak PG, Davis JM, Preskorn SH, et al. Treatment with antidepressants. In: Mitchell CW, Kairis LR, Glazer A, et al. Principles and Practice of Psychopharmacotherapy, 4th edn. Philadelphia: Lippincott Williams & Wilkins, 2006.
22. Hetrick S, Merry S, McKenzie J, Sindahl P, Proctor M. Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents. Cochrane Database Syst Rev2007;CD004851.