

## Original Article

## Case Study: Assessment and Management of Medication Induced (DULOXETINE) Abnormal Involuntary Movements.

*Sadaf Amir, MD; Syed Jamal Mustafa, MD; Khalid Ahmed, MD, Syed Kamal Mustafa, MD.*

## ABSTRACT:

The awareness of the occurrence of mental health illness in younger age group has substantially increased in recent years, consequently so have the prescriptions of psychotropic medications at midlevel, primary care and specialty care level. In any given month in most cities in the USA which have an active Pharmaceutical representative community, practitioners are exposed to branded information studies talking about the benefits of second generation atypical psychotropic medications. Also being highlighted is their proposed role in numerous mental health diagnosis, from Schizophrenia, to Depression, to Autism, to various phases of Bipolar Disorder. It is acknowledged that the pharmaceutical agents available today are vastly superior in their effectiveness (both efficacy and tolerability) as compared to their predecessors (first generation/Typical Anti-psychotics), however this piece of information should not cause the Doctors and Practitioners to lower their guard when it comes to judicious and appropriate use of such pharmaceutical agents. Various side-effects are discussed in Package Inserts, as well as print and electronic versions of prescribing aids and tools including, PDR, Epocrates etc. Despite the fact that they are not very common, the risk of movement disorders should be cautiously evaluated before prescribing or augmenting with anti-psychotic medications, and monitoring of abnormal movements needs to be done more frequently. Another very important factor to consider is the fact that due to overwhelming shortage of Trained Psychiatrist, and the phenomenal increase in the mental health needs in children, adolescent and adults (young and old), therefore those non-psychiatric Prescribers who prescribe Psychiatric Medications, including Primary Care, Family Practice and Pediatric Physician, as well as mid-level providers (Nurse Practitioners and Physician Assistants) should be trained more thoroughly with more exposure and supervised training according to current guidelines. The following case brings to light the complexities of assessing and then managing medication induced Abnormal Involuntary Movements.

### CASE REVIEW:

This case is of a 24-year-old white male, being treated in an outpatient setting, for paranoid schizophrenia, with additional symptoms of inattention, distractibility and feelings of anxiety and being on edge; who was psychiatrically stable for the past three years on his medication regime of GEODON, ADDERALL and NEURONTIN. Patient also had a past history of alcohol use, which is in early remission at present (American Psychiatric Association, DSM-5, 2014).

The patient presented to the clinic six days after having initially developed jaw pain that evolved over the next two days, into abnormal involuntary movements of the jaw and possibly tongue. The unscheduled appointment, was requested by the patient's mother who was concerned about the patient being in obvious distress after taking one only dose of DULOXETINE which was prescribed by his Primary Care Physician, to address depression symptoms that he had reported to the PCP during a routine visit.

The patient and mother were also concerned that the abnormal movements had not remitted despite the medication (DULOXETINE) having been discontinued by the patient. The patient reports that during the past six days, he had visited the local hospital Emergency

Department once, where a dose of BENADRYL was administered with only brief (2-3 hours) relief from the symptoms.

On examination abnormal involuntary movements manifested by continuous noticeable opening and closing of jaw and possible writhing movement of tongue inside mouth were observed (Bucco-Oro-Masticatory). The movements were causing functional deficits such as difficulty speaking and to some degree swallowing. The patient's mother reported that the movements diminished while the patient was asleep, and were noticeably exacerbated by physical exercise, anxiety and stress. The movements created emotional disturbances such as fearfulness, low mood, and feelings of hopelessness in the patient.

After a review of history and systems, and examination; a provisional diagnosis of drug-induced dystonic reaction, "Acute Oro-Mandibular Dystonia" was made, other causes of dyskinesia were also considered and systematically excluded (J.Milstein, 2013). The patient and family wanted medication regime to be changed, to provide relief. As no definitive answers were available, the theory of what might have occurred and what medications could potentially be beneficial to the patient was explained in detail to the patient and patient's mom. After obtaining informed consent treat-

## Original Article

ment was initiated with LORAZEPAM, NEURONTIN, COGENTIN and VITAMIN-E. The patient tolerated the regime. The response to treatment as evidenced by amelioration of symptoms was slow but noticeable. By the end of six months there was no observable abnormal involuntary movement.

**DISCUSSION:**

In a review of U.S. Food and Drug Administration Adverse Event Reporting System was researched and it was found that 89 patients with antidepressant induced Extra Pyramidal Symptoms had been reported between 2005 and 2008. Fifty-nine of the reported cases were due to duloxetine (Albayrak & Ekinci, 2012), and 6 of them had acute dystonia (J.Milstein, 2013). There have been several case reports of acute dystonia in patients who were treated with antidepressant agents (Stahl S. M., 2014) (Alan F. Schatzberg & Charles DeBattista, 2013) such as fluvoxamine, sertraline, fluoxetine, citalopram, mirtazapine, paroxetine, venlafaxine and bupropion. (Görkem Karakaş Uğurlu, 2013)

A case of Duloxetine induced tardive dyskinesia was reported in a 62-years- old female with Major Depressive Disorder who developed dyskinesia when she was in her fourth month of treatment with duloxetine. The dyskinesia was reported to have remitted with Fluvoxamine. (Albayrak & Ekinci, 2012)

Another case of tardive dystonia and tardive dyskinesia was reported in a 58-year-old female with major depressive disorder, who developed distressing oral dyskinesia, mandibular dystonia after treatment with duloxetine (30–60 mg per day) for 18 months. Despite discontinuation of duloxetine, she only had partial remission. (Pei-Yi Chen, 2010)

The authors of another article titled as “extrapyramidal symptoms associated with antidepressants” concluded after review of the literature and analyzing case reports that it is essential to recognize that EPS have been reported with different classes of antidepressants (SSRIs, SNRIs, NDRIs), are not dose related, and can develop with both short-term and long-term use. (Subramoniam, MD Lada, MD Renata, & MD Ronald, 2010)

In the above mentioned cases, the monotherapy suggested that duloxetine was directly associated with dyskinesia. In contrast the patient case report presented in our case was being prescribed polypharmacy, which made associations difficult to determine.

The authors in the case being presented also made an attempt to investigate whether it was a drug interaction or duloxetine itself that was primarily responsible for the dystonia?

In summary; Duloxetine (Cymbalta) increases Serotonin and Nor-epinephrine by presynaptic reuptake inhibition of Norepinephrine and Serotonin. Whereas Ziprasidone (Geodon) increases Dopamine by antago-

nism of Dopamine D2 receptor and Serotonin 5HT2A receptor. (Stahl S. M., 2013). Amphetamine Salts (Adderall) increase Dopamine and Nor-Epinephrine in prefrontal cortex by (i) Presynaptic reuptake inhibition of Norepinephrine and Dopamine and (ii) increasing presynaptic Dopamine release. (Stahl S. M., 2013). Gabapentin (Neurontin) increases GABA by (i) increasing the transport of GABA through Blood Brain Barrier, (ii) increasing GLU-DE (Glutamic Acid Decarboxylase; the enzyme needed for converting Glutamic Acid to GABA) and (iii) inhibiting GABA- T (GABA-Transaminase; the enzyme needed for catabolism of GABA) (Mark A. Frye)

Dystonia (lit, abnormal muscle tone) is a neurological condition characterized by involuntary and sustained muscle spasms that can force affected parts of the body into abnormal movements or postures. Unlike other movement disorders, which result from unopposed contractions of a muscle group (chorea) or alternating contractions of agonist and antagonist muscle groups (tremors); dystonias results from the simultaneous contractions of agonist and antagonist muscle groups. (J.Milstein, 2013)

**PATHOPHYSIOLOGY OF ACUTE DYSTONIC REACTIONS:** The exact pathophysiology of acute dystonic reactions remains unknown. (Görkem Karakaş Uğurlu, 2013). However there are theories that deserve out attention as to the possible etiology of Dystonias, which aid us in formulating a comprehensive management plan. The various theories could be any one of the following;

Lack of Dopamine. The temporal relationship to dopamine blockade suggests that lack of dopamine activity may cause dystonic reactions. However this theory does not explain why antidepressant like SSRI and SNRI cause dystonic reaction.

Dopamine Blockade induced Positive Feedback Loop. In response to drug-induced dopamine blockade, a feedback loop may provoke an imbalance in secretion of dopamine or a dopamine-like neurotransmitter that may lead to dystonic movements.

Excessive Cholinergic Activity. Favorable responses to anti-cholinergic medications suggest that excessive cholinergic activity may have a role to play in dystonic movements.

The exact mechanism of causation of duloxetine and other antidepressant-associated dystonia is unknown (Subramoniam, MD Lada, MD Renata, & MD Ronald, 2010). Plausible mechanisms may include inhibitory modulation of dopaminergic functions in the nigrostriatal pathways; the reciprocal balance between dopaminergic, serotonergic, noradrenergic, or cholinergic activity.

**MANAGEMENT APPROACH**

Irrespective of what might be the causative factor in Dystonia, the uphill and daunting task of the physician

## Original Article

remains to provide management i.e. comfort, support and treatment.

Management of Dystonia is a multi-step process, unfortunately with no guarantees.

### STEP ONE: RISK FACTOR ASSESSMENT:

The risk factors for dystonic reactions include younger population, male gender, comorbid psychiatric illnesses, co-morbid substance abuse, previous ECT, and pre-existing brain damage. In particular, individuals who have abused cocaine place themselves at a 40-fold increased risk of developing acute dystonic reactions to antipsychotics. (J.Milstein, 2013)

The patient cited in this case report is a young male, with a history of alcohol and nicotine use.

### STEP TWO: DETERMINE THE DIAGNOSIS:

If the patient truly has Dyskinesia, then it is also imperative to determine the onset type; acute onset or tardive onset. Psychotropic medication-induced movement disorders (dyskinesias) are generally divided into these two groups based on the onset of abnormal involuntary movements. In this classification, (J.Milstein, 2013) Acute Dyskinesias develop within days, whereas Tardive (late) Dyskinesias may take as long as up to 6 months or more to manifest after exposure to the offending agent.

The patient in the case report appeared to have an acute onset of dyskinesia following use of Duloxetine.

### STEP THREE: DETERMINE THE TYPE OF DYSKINESIA; FOCAL OR GENERALIZED?

Focal dystonia generally involves the face or neck, and typically presents with blepharospasm, oromandibular dystonia, platysmal contractions, and emotional disabilities that have been reported to be associated with varying degrees of laryngospasm, and spasmodic. Generalized Dyskinesias are not limited to the above patterns, although they are also associated with emotional disturbances.

The patient in our case report, presented with symptoms indicating Acute Onset Focal Oro-Mandibular Dyskinesia.

Oro-mandibular dystonia consists of prominent contractions of the lower facial muscles and jaw muscle it is important to differentiate between Oro-Mandibular Dystonia and Oral-Buccal-Lingual Dystonias (of Tardive Dyskinesia) Although not definitive, it can be at times be distinguished from tardive dyskinesia by the symmetric involvement and absence of tongue protrusions. (Görkem Karakaş Uğurlu, 2013) (J.Milstein, 2013).

### **MANAGEMENT:**

Management of Dyskinesia start methodically. Usually the first step is to stop the potentially noxious agent/offending agents. In the case in review it could have

included Geodon, Adderall, and/or Duloxetine.

Following the discontinuation of the offending agent, supportive therapy and medication regime is initiated.

The treatment regime initiated for the case in review, is the Puget Sound Psychiatric Center Dyskinesia Treatment Protocol (PDTP) utilized at the Puget Sound Psychiatric Center. (Syed Jamal Mustafa, 2002). The details of the protocol is beyond the scope of this case review.

The PSPC Dyskinesia Treatment Protocol calls for an aggressive approach with medications; Benzodiazepines, Benzotropin, Gabapentin and Vitamin-E.

**BENZODIAZEPINES:** Patient was started on Ativan (Lorazepam) for four weeks that was later switched to Diazepam. The Diazepam taper off, later on, was relatively smooth due to its long half-life and milder withdrawal symptoms. Benzodiazepines were started with rationale of having multiple actions such as anxiolytic, muscle relaxant, anticonvulsant and sedative-hypnotic effects that will be helpful in treating movement disorder.

The mechanism of action of benzodiazepines involves modulation of GABAergic activity by acting on the GABAA-benzodiazepine-Cl<sup>-</sup> complex, known to contain multiple modulatory binding sites and many receptor subtypes. (Seiji Nishino, 2009)

Care has to be taken when prescribing Benzodiazepines because of patient's history of alcohol dependence, currently in early remission.

**BENZTROPINE (COGENTIN):** Dystonia is thought to be triggered by imbalance between dopamine and acetylcholine at nigrostriatal pathway. (Benjamin James Sadock, 2007). Some psychotropic medications (especially antipsychotics) decreases dopamine and may increase acetylcholine. Anticholinergic medications such as Benzotropine Mesylate (Cogentin) was used to counter this cholinergic effect.

**GABAPENTIN (NEURONTIN):** Gabapentin has been used off-label for numerous conditions, including movement disorders (like ALS, essential tremors and Parkinson disease) anxiety, mood stabilization, alcohol withdrawals, sleep disturbance. The wide range of indications, few side effects and minimal drug-drug interactions make it a good choice for symptom control in our patients.

Gabapentin increases brain GABA by an amino acid active transporter at the blood-brain barrier. Gabapentin increases intracellular GABA by multiple enzymatic regulatory mechanisms. It increases the synthesis of GABA by increasing activity of glutamic acid decarboxylase and decreases GABA degradation by inhibiting GABA-transaminase. (Seiji Nishino, 2009)

**VITAMIN E:** Vitamin E is an antioxidant that binds with free radicals possibly produced by chronic use of psy-

## Original Article

chotropic medications. (Seiji Nishino, 2009)

**CONCLUSION:**

From this case it can be easily inferred that involuntary movements can develop for a variety of reason, and very rapidly at times. Once developed they lead to a great deal of anguish and agony both for the patient and their family and also for the treating Physician.

The unpredictable nature and uncertain outcome despite the best of treatment approaches further enhance the stress experienced by everyone involved in the treatment and management of such cases.

It should be emphasized that, because of the great variability in Dystonia, there are no universally accepted standardized successful guidelines to treat the acute dystonias, or those that may go on to become chronic.

Chances that a physician will encounter situations in which their patient will develop movement disorders is great and the odds continue to increase as exposure of our patients to various risk factors increases. Although the exact numbers are not available, it is fair estimation to consider that the risks might be almost approaching the same rate/ratio seen when the earlier generation anti-psychotic medications were used. One reason for predicting such a high rate is based on the sheer number of anti-psychotic prescriptions written in the current era as compared to the past.

The treatment approach used by the authors in treating this patient was the Puget Sound Psychiatric Center Dystonia Treatment Protocol, the patient was fortunate that the treatment protocol in his case was successful, with good results. However the real-world limitation is that not all results are perfect, and more understanding and research needs to be conducted to continue to create better treatment protocols.

Apart from the medication aspect of the Treatment Protocol, other factors that are equally important in successful outcome include, (i) strong family support (ii) supportive psychotherapy (iii) frequent phone contact (iv) frequent office visits and examinations, and (v) positive and optimistic outlook by the treating doctor. One key aspect to remember is that patient does better when clinicians are able to maintain an optimistic, empathic, and helpful approach.

Clinicians, especially primary care physician, need to remain aware of the fact that even the so called benign antidepressant medications can cause dyskinesias. And that this particular side effect should also be discussed with patients along with other side effects before starting such medication. Additionally, providers needs to be careful about drug-drug interactions in this era of poly-pharmacy.

Baseline and six-monthly examination for abnormal involuntary movement disorders should be considered for all patients who are on medications with high risk of

involuntary movements. Checking drug interactions and educating patients and families about benefits as well as being honest about potential adverse effects is absolutely essential. It is also important that alternate treatment options need to be discussed so that informed decisions are made by the patients. This approach increases patient participation in decision making. It is also important to identify and address any adverse effects as early as possible.

**References:**

- Alan F. Schatzberg, M., & Charles DeBattista, D. M. (2013). *Antidepressants*. Arlington: American Psychiatric Publishing.
- Albayrak, Y. M., & Ekinci, O. M. (2012, October). Duloxetine-Associated Tardive Dyskinesia Resolved With Fluvoxamine: A Case Report. *Journal of Clinical Psychopharmacology*, 32(5), p 723–724.
- American Psychiatric Association. (2014). *Diagnostic and Statistical Manual-5*. American Psychiatric Association Press. ISBN 0890425558.
- Benjamin James Sadock, M. V. (2007). *Kaplan & Sadock's Synopsis of Psychiatry* (Tenth ed.). New York.
- Görkem Karakaş Uğurlu, S. Ö. (2013). Acute Dystonia after Using Single Dose Duloxetine: Case Report. *US National Library of Medicine National Institutes of Health*.
- J. Milstein, D. M. (2013). *Clinical Neurology for Psychiatrists*. Bronx, NY: Elsevier Saunders.
- Mark A. Frye, M. K. (n.d.). Chapter 38. Gabapentin and Pregabalin. In M. C. Alan F. Schatzberg (Ed.), *The American Psychiatric Publishing Textbook of Psychopharmacology, Fourth Edition*. Arlington, VA, USA: American Psychiatric Publishing.
- Pei-Yi Chen, M. P.-Y.-C.-Y. (2010). Duloxetine-related tardive dystonia and tardive dyskinesia: a case report. *Psychiatry research*, 32(6), 646.e9–646.e11.
- Sandhya Norris, M. P. (n.d.). Chapter 23. Duloxetine and Milnacipran. In M. Alan F. Schatzberg, & M. P. Charles B. Nemeroff (Eds.), *The American Psychiatric Publishing Textbook of Psychopharmacology*.
- Seiji Nishino, M. P. (2009). *The American Psychiatric Publishing Textbook of Psychopharmacology* (Fourth Edition ed.). Arlington, VA.
- Stahl, S. M. (2013). *Stahl's Essential Psychopharmacology* (Fourth ed.). New York: Cambridge University Press.
- Stahl, S. M. (2014). Modulating the serotonin system in treatment of major depressive disorder. *CNS Spectrums*, 57-67.
- Subramoniam, M., MD Lada, A., MD Renata, S., & MD Ronald, B. (2010). Extrapyramidal symptoms associated with antidepressants—a review of the literature and an analysis of spontaneous reports. 22.
- Syed Jamal Mustafa, M. (2002). *PSPC Dyskinesia Treatment Protocol*. Bothell: PSPC Dyskinesia Treatment Protocol.