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Letter to the Editor

Amisulpride Induced Oropharyngeal Dyskinesia in a patient with Schizophrenia: A case report and review of literature

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Dear Sir,

Amisulpride is a second-generation (atypical) antipsychotic; used as first line treatment for schizophrenia and other psychotic disorder (McKeage and Plosker, 2004). It has a high affinity for dopamine (D3/D2) receptors resulting in a dose-dependent modulation of dopamine activity (Scatton et al., 1997). Amisulpride binds preferentially to D2/D3 pre synaptic auto receptors at a lower dose range from 100 to 300 mg, increasing dopaminergic transmission in the prefrontal cortex. It antagonises postsynaptic dopamine receptors at the dosages between 400 and 800 mg/day. The occurrence of the extrapyramidal side effects ranging from dystonia to Tardive Dyskinesia (TD) could be due to blockage of postsynaptic dopamine receptors at higher dosages of amisulpride. There are many case report level evidence for amisulpride associated Tardive Dyskinesia. The definitive etiopathogenesis of tardive dyskinesia is not known. One popular theory is chronic exposure to the neuroleptics results in D_2 receptor upregulation with postsynaptic dopamine receptor supersensitivity. The prevalence of TD is 15%–30% in patients on long-term treatment with Antipsychotics. The prevalence is higher with typical antipsychotics (32.4%) (Yassa and Jones, 1985) compared with second-generation (atypical) antipsychotics (13.1%) (Kim, Macmaster, and Schwartz, 2014). In this communication, we report a male patient with Schizophrenia who developed tardive dyskinesia on a stable dose of amisulpride and remitted following a switch to clozapine.

Patient was a 39-year-old married male, who completed diploma in civil engineering. He had a good premorbid functioning, with nil significant past, family history of psychiatric and neurological illness. Patient had insidious onset continuous illness of 2-year duration with phenomenology suggestive of referential and persecutory delusions, made phenomenon, thought broadcasting phenomena with significant biosocial occupational dysfunction. Diagnosis of Schizophrenia (F20) was made as per the International Classification of Diseases – 10 (ICD –10), 10th edition. Patient was on treatment with Tablet Amisulpride 400 mg/day. His psychotic symptoms improved within two months of outpatient treatment.

Patient and his family started noticing abnormal involuntary movements after 4 months of initiation of amisulpride; they were, non-purposeful, non-rhythmic movements involving perioral muscles, tongue, muscles of mastication, peri orbital muscles and right upper limb. These abnormal involuntary movements appeared in the form of difficulty in closing the mouth, sudden tightening of lips, puckering movements, protruding movements of the tongue, involuntary movements of the uvula. These movements resulted in difficulty in chewing, swallowing, and difficulty in speaking fluently. He did not have any difficulty in initiating the speech but speech would become increasingly difficult when he would try to talk faster, then he takes pause and resume talking. These movements were observed to be absent in sleep, minimal at rest and increased as the patient performs any activity but were most pronounced when he eats, drinks and talks. Because of these movements, he was unable to communicate, eat, swallow properly, and lived in fear of social embarrassment.

Patient was evaluated by a private psychiatrist and was diagnosed with Tardive Dyskinesia and Schizophrenia in remission. He was treated with Tablet Aripiprazole 15 mg and Amisulpride was stopped. When Tardive Dyskinesia persisted, he was adequately tried on Tablet Tetrabenazine, Tablet Clonazepam and Cap. Vitamin E supplements. However, he didn't show any response to it. Therefore, he was referred to us for further evaluation and treatment. The detailed physical examination by us, showed no focal deficits, except Oro Pharyngeal Tardive Dyskinesia. The Abnormal Involuntary Movements Scale (AIMS) score was 28. On mental status examination, no psychotic symptoms were elicited.

All the investigations were within normal limits including serum ferritins, serum ceruloplasmin, 24 h urine copper level and peripheral smear for Neuroacanthocytosis, except low vitamin B12 level and a higher level of Homocysteine as shown in Table 1. The Magnetic Resonance Imaging of Brain Plain and contrast was done which revealed Calcification on left Basal ganglia with mild rim enhancement. Findings were discussed with neuro radiologist and concluded that MRI – Brain finding were inconclusive and would not explain the oropharyngeal dyskinesia. Above investigations were done to rule out movement disorder including Wilson's disease and Neuroacanthocytosis, so the possibility of Amisulpride induced oropharyngeal dyskinesia was considered.

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Table 1
Lab Investigations.

S.NO.	Investigation	Result (reference range)
1)	24 h' urine copper	84 ug (< 70ug/24 h being Normal)
2)	S. Ceruloplasmin	28.4 (15–35 mg/dl)
3)	S. Copper	105.5 (70–150 ug/dl)
4)	S. Homocysteine	91.46 (< 15 umol/L)
5)	S. Vitamin B12	93 pg/ml (180–914 pg/ml)
6)	Liver function tests	WNL
7)	Renal function tests	WNL
8)	Thyroid function tests	WNL
9)	Complete blood counts	WNL
10)	Peripheral smear	Neuroacanthocytosis is negative
11)	Fasting glucose	WNL
12)	Electrocardiogram	Normal sinus rhythm

Clozapine was started with 12.5 mg and gradually increased to 100 mg/day after informed consent on outpatient basis. The periodic haematological test was done. He has shown improvement in dyskinesia after 2 months of initiation. His improvement was remarkable and sustained after 6 months, and 12 months of discharge and AIMS score reduced to 10/40, 5/40 respectively. He has returned to his job without dyskinesia interfering in socio-occupational functioning. The patient and family perceives 95% improvement with respect to dyskinesia and psychotic symptoms are still in remission.

In the literature, there are few case reports, where amisulpride was used for the treatment of dyskinesia due to antipsychotics and withdrawal dyskinesia with amisulpride. It is hypothesized that it might help in TD in low dose by lowering D_2 binding index in basal ganglia. In contrary to that; there were many published reports on amisulpride-induced dyskinesia. It might be due to dose-dependent modulation of dopamine activity of amisulpride. At higher dose, it blocks postsynaptic dopamine receptors, preferentially in basal ganglia resulting in extrapyramidal side effects ranging from dystonia to Tardive Dyskinesia (TD).

Table 2 shows published case reports on amisulpride-induced dyskinesia. Many were young adults; suffering from schizophrenia. The average duration of treatment taken to develop Tardive Dyskinesia varied from a minimum of 12 weeks to 60 weeks. In one case, tardive dyskinsia developed at 100 mg and other six cases were on 400 mg and above doses. When it comes to common regions involved in amisulpride induced TD, four cases had dyskinetic movements of oro-facial and neck region, two cases had involvement of peripheral extremities and in one case ocular region was effected. The symptoms ameliorated following switching over to clozapine in three patients and switching over to quetiapine in three patients. In one case, tardive movement reduced after tapered and stopping Amisulpride. In all cases reported and our patient, they don't have any well-established risk factors like affective disorder, previous brain injury, pre-existing Parkinsonism, and alcoholism, which were described in the literature (Mathews et al., 2005). In our patient, he had been under treatment with amisulpride, which is a high potent, atypical antipsychotic for schizophrenia. Four months after the initiation of amisulpride, he developed oropharyngeal dyskinesia. These movements persisted even after discontinuation of amisulpride and changing over to aripiprazole. After two months of initiation of Clozapine, dyskinetic movements improved significantly. Onset of dyskinetic movements in our patient was associated with amisulpride administration. It could be speculated that this result is simply a new onset of dyskinetic movements following the administration of a high potency dopamine antagonist for long period. In our case the Naranjo ADR Scale score was 6, suggesting that the adverse event was probably caused by Amisulpride (Naranjo et al., 1981). This case report adds to the evidence of an association between higher doses of amisulpride use and Tardive dyskinesia.

Disclosure

No conflicts of interest in this work.

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Table 2
Sociodemographic and clinical characteristics of patients with Amisulpride (AMS) associated Dyskinesia.

Sl No	Case reports/Letter to Editor	Age in years	Sex	Diagnosis	AMS Dosage	Duration of AMS exposure before the onset of Tardive Dyskinesia	Type of Tardive Dyskinesia movements	AIMS Score	Treatment Alternative considered
1)	Fountoulakis et al., 2006	34	Male	Schizophrenia	400mg	60 weeks	Orofacial, neck, trunk dyskinetic movements		Symptoms were ameliorated with stopping Amisulpride, changed over to quetiapine 1200mg
2)	Goyal and Sinha, 2010	14	Male	Schizophrenia	600mg	12weeks	Dyskinetic movements in left finger, wrist, arm and leg	6	ameliorated by reducing the Amisulpride to 400mg
3)	Guriz et al., 2010	33	Male	Schizophrenia	400mg	54weeks	Tardive Dystonia of neck muscle	–	Symptoms were ameliorated with stopping Amisulpride, changed over to quetiapine 600mg
4)	Masdrakis et al., 2007	37	Female	Schizophrenia	800mg	26weeks	Oral–buccal–lingual dyskinetic movements		ameliorated with stopping Amisulpride, changed over to quetiapine 300mg
5)	Mendhekar and Andrade, 2009	24	Male	Schizophrenia	400mg	15 weeks	Dyskinetic finger movements in both hands	9	Symptoms were ameliorated with stopping Amisulpride, changed over Clozapine 200mg
6)	Mendhekar et al., 2010	22	Female	Schizophrenia	400mg	18 Weeks	Tardive oculogyric crisis	–	Symptoms were ameliorated with stopping Amisulpride, changed over Clozapine 200 mg
7)	Tharoor and Padmavati, 2013	56	Female	Mixed Anxiety and Depression	100mg	12 weeks	Orofacial dyskinetic movements	15	Not responded with tetrabenazine, so Clozapine was considered

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Guru S. Gowda*, Leela Shanker Sastry Nagavarapu, Shiva Shanker Reddy Mukku, Syed Farooq Ali
Department of Psychiatry, National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore, 560029, India
Department of Clinical Neuro Sciences, National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore, 560029, India
E-mail address: drgsgowda@gmail.com

* Corresponding at: Department of Psychiatry, National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore, 560029, India.