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Evaluation of Tardive Dyskinesia in Aged Schizophrenics by Means of Abnormal Involuntary Movement Scale: A Pilot Study

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Abstract

Introduction: Tardive dyskinesia (TD) includes involuntary choreiform or athetoid movements of the jaw, lower face, tongue, and extremities, developing in association with the use of an antipsychotic medication, and may develop in about 20 to 40 percent of patients who require long-lasting hospitalization. In the present study, the prevalence of this condition has been measured among an elderly group of schizophrenic patients.

Methods: One hundred and one elderly schizophrenic patients, who were hospitalized in the chronic section of a community psychiatric hospital, were selected for the present cross-sectional study. Abnormal Involuntary Movement Scale (AIMS) was employed to screen for patients with schizophrenia who also had TD. Scale for Assessment of Positive Symptoms, Scale for Assessment of Negative Symptoms, Schedule for Assessment of Insight, and Clinical Global Impressions – Severity of illness, as well, had been used as ancillary scales for evaluation of severity of general psychopathology of schizophrenia, and comparing the TD patients with the group of patients without TD, for probing the intervening parameters.

Results: While abnormal movements were clear in 38.61% (n=39) of elderly schizophrenic patients, only seven of them (6.93 %) could be diagnosed as TD, based on the above-mentioned criteria. All of them were using conventional antipsychotic medications, accompanied with anticholinergic medications. Among TD patients, three cases had only abnormal facial and oral movements, one patient had atypical facial and oral movements as well as anomalous extremity movements, one patient had irregular facial and oral movements in addition to unusual trunk movements, and lastly, two patients had nonstandard extremity movements. In addition, around 71% of patients with TD were aware of their unusual movements. Between-group analysis did not show any significant difference between patients with TD and patients without TD in age, duration of illness, positive symptoms, negative symptoms, insight, and general psychopathology.

Conclusion: According to the findings of the present study, the prevalence of Tardive Dyskinesia among elderly schizophrenic patients, who were using typical antipsychotic medications, is lower than what has been indicated thus far.

Keywords: Schizophrenia; Typical Antipsychotic Drug; Atypical Antipsychotic Drug; Extrapyramidal symptoms; Tardive Dyskinesia; Medication Induced Movement Disorder

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Introduction

Tardive dyskinesia (TD) includes involuntary choreiform or athetoid movements of the jaw, lower face, tongue, and extremities, developing in association with the use of an antipsychotic medication for at least a few months, though symptoms may appear after a shorter period in older persons. In some patients, movements of this kind may appear after cessation, or after alteration or decrease in dosage of antipsychotic drugs. Tardive syndrome includes other forms of movement complications, such as akathisia or dystonia, which are distinguished by their late appearance in the course of management and their potential perseverance for months to years, even despite antipsychotic discontinuation or dosage lessening [1]. TD can appear in various ways. Initial clinical symptoms are primarily messy movements in the facial areas, mouth and tongue, which seem uncontrollable and repetitive. Also, TD symptoms can affect movement of the torso, limbs, head and neck, and patients with severe disorders may also suffer from vague speech, abnormal postures and problematic swallowing [2]. The severity of the movements may range from slight to obviously incapacitating. TD is worsened by stress and vanishes during sleep [3]. TD develops in about 10 - 20 percent of patients who are treated for more than a year. About 20 - 40 percent of patients who require long-standing hospitalization have TD [4,5]. The occurrence of TD can also depend on whether the antipsychotic drug is atypical or typical, with around 13.1% incidence with atypical antipsychotic medications and about 32.4% rate with typical antipsychotic drugs [6,7].

Females, children, patients who are more than fifty years of age, and patients with brain injury or affective disorders are at higher risk [8,9]. Increased antipsychotic medication exposure (particularly typical antipsychotics), African-American ethnicity, cognitive disturbance, alcohol or substance abuse, early occurrence of drug-induced parkinsonism, diabetes, and HIV, as well, have been accounted as other risk factors for the development of TD [10,11]. Moreover, drugs used to treat Parkinson's disease can cause TD [12,13] (Table 1). Up to now, sustained D2 receptor blockade resulting in receptor hypersensitivity is the most common theory explaining the development of TD. Besides, genetic studies have indicated a possible relationship with polymorphisms in the DA2 receptor, DA3 receptor, dopamine transporter (DAT1), and the serotonin 2A receptor genes. Oxidative stress and cell demise secondary to augmented glutamatergic neurotransmission triggered by blockade of presynaptic dopamine receptors is also hypothesized [14-18]. Although proof proposes a genetic susceptibility to TD [19], evidence suggests that a genetic protection against TD exists [20,21]. Furthermore, some studies suggest that D3, D4, and D5 receptors are also involved in the pathogenesis of TD [22]. Since anticholinergic agents are also associated with TD, an imbalance of acetylcholine and dopamine is likely involved in TD pathogenesis [23]. While usage of adjunctive agents, like vitamin B6, procholinergic agents (e.g., donepezil [Aricept]), Ondansetron (Zofran), a selective 5-HT3 receptor antagonist, cyproheptadine (Periactin), a 5-HT and histamine antagonist, and levetiracetam (Keppra) is of limited benefit [24] (Table 1), the use of deep brain stimulation for severe and refractory TD offers hope to those who are

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rigorously incapacitated [24]. Among patients with schizophrenia, the life quality of patients with TD may drop radically [25], and leads to a decline in patients' social functioning, and may affect quality of life and treatment compliance meaningfully [26]. Additionally, TD can increase the difficulty in handling the primary disorder, thus increasing the economic burden on the patient's family [27]. Currently, appropriate proof for effectiveness exists for two Vesicular monoamine transporter 2 (VMAT2) inhibitors, valbenazine and deutetrabenazine [28,29]. Among them, Valbenazine was the first drug that has been approved for TD in the United States [30,31].

Methods

One hundred and one elderly male patients (≥ 55 years old), who received a diagnosis of schizophrenia, according to the 'Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5)' (1), and were hospitalized in the chronic section of a community psychiatric hospital in south of Tehran, had been selected for the present cross-sectional study, which had been performed in April 2014. While the study was carried out consistent with the 'Declaration of Helsinki and Ethical Principles for Medical Research Involving Human Subjects' [32], the patients were informed about the procedure, and a signed informed consent was received from those who were interested in participating in the study or from a legal guardian or representative. Abnormal Involuntary Movement Scale (AIMS) was used to assess the severity of TD in patients who were diagnosed with schizophrenia. AIMS is a 12-item tool developed at the National Institute of Mental Health (NIMH) and has been utilized by clinicians to give a numeric measure to the observed atypical movements in various sections of the body [33,34]. The AIMS has a global rating of severity, a rating of incapacitation because of the irregular movements, and an evaluation of the patient's attentiveness to the atypical movements. Moreover, it can be used to measure anomalous movements in different types of patients, including adults, children, and adolescents. The scale can be done as part of a physical-neurological examination by a trained clinician. The AIMS does not make the diagnosis of the disorder causing the movement abnormality unless some criteria have been established already to ease the diagnostic process. The Schooler–Kane research criteria are commonly used to find probable antipsychotic-induced TD, and need that three criteria are met: (1) symptoms occur after at least 3 months of treatment with an antipsychotic, (2) abnormal, involuntary movements must occur in 2 or more body regions if mild, or 1 body region if moderate to severe, as determined by a rating scale such as the AIMS, and (3) there are no other conditions that may have caused the abnormal movement patterns [35]. So, in the present appraisal, patients whose abnormal involuntary movements were induced by medical or neurological diseases were excluded. Scale for Assessment of Positive Symptoms (SAPS) [36], Scale for Assessment of Negative Symptoms (SANS) [37], Schedule for Assessment of Insight (SAI) [38], and Clinical Global Impressions – Severity of illness (CGI-S) [39], as well, had been used as ancillary scales for evaluation of severity of general psychopathology of schizophrenia, and comparing the TD patients with the group of patients without TD, for probing the intervening parameters.

Statistical analysis

Baseline characteristics were compared by 't tests' for continuous variables. Between-group analysis, too, with respect to ancillary scales, like SANS, SAPS, SAI, and CGI-S, was performed by 't tests'. Statistical significance is defined as P-value ≤0.05. 'Med-Calc' statistical software, version 15.2, was the statistical software tool for analysis.

Results

While abnormal movements were clear in 38.61% (n=39) of elderly schizophrenic

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patients, only seven of them (6.93 %) could be diagnosed as TD, based on the above-mentioned criteria. Medication induced Extrapyramidal adverse effects, like Parkinsonism or tremor, and other abnormal movements like Tic, Chorea, Myoclonus, Ballismus and rigidity, which were present either before initiation of illness or in advance of prescription of neuroleptic, or were generated later due to comorbid medical or neurological ailments, constituted the rest of abnormal movements in the present sample of aged schizophrenic patients. Among the said group with TD, and based on the assessment by AIMS, three patients had only abnormal facial and oral movements with minimal to mild severity (code: 1-2), one patient had atypical facial and oral movements in addition to odd extremity movements with mild to moderate (code: 2-3) and minimal to mild severity (code: 1-2), respectively, one patient had anomalous facial and oral movements in addition to irregular trunk movements with minimal to mild (code: 1-2) and mild to moderate severity (code: 2-3), respectively, and lastly two patients had unusual extremity movements with minimal to moderate severity (code: 1-3). While two of them, one patient with abnormal extremity movements and the other patient with atypical facial and oral movements, had problems with teeth, the rest of the patients usually wore dentures. In addition, in the present survey, around 71% of patients with TD were aware of their unusual movements. In this regard, while two patients with only anomalous facial and oral movements had no awareness of their odd movements (code: 0), one of the patients in the said cluster was aware of mild distress (code: 2).

Two patients with irregular extremity movements were aware of the uniqueness of their atypical movements, with mild distress in one of them (code: 2) and no distress in the other one (code: 1). The patient with abnormal facial and oral movements plus atypical trunk movements was aware of moderate distress (code: 3). The same was applicable, as well, for the patient with nonstandard facial and oral movements in addition to strange extremity movements. Nevertheless, none of them could be considered as severely incapacitated due to the said abnormal movements. All of them were using conventional antipsychotic medications, like chlorpromazine, haloperidol, perphenazine and trifluoperazine [Mean ± SD mg/d Chlorpromazine equivalent = 464.28±118.66], in companion with anticholinegic medications (biperiden or trihexyphenidyl). While between-group analysis did not show any significant difference between patients with TD and patients without TD about some demographic parameters, like age and duration of illness, no significant difference, as well, was evident between them with respect to measuring positive symptoms, negative symptoms, insight, and general psychopathology, which had been assessed by the said ancillary scales (Table 2).

Discussion

Medication-induced TD is a complex and distinctive neurologic condition [40]. While the reported incidence of TD seems to be reduced with the usage of atypical antipsychotic drugs, the risk of developing TD remains with these medications. Furthermore, several other medication classes have a high prevalence of TD and yet are not commonly considered to be TD-inducing [41-43]. Drug-induced Parkinsonism and TD are stigmatizing movement disorders linked with exposure to dopamine receptor blocking agents such as antipsychotic drugs, but they differ in their pathophysiology and clinical management. Treatment for one may exacerbate the other, and there are important diagnostic signs that help in making a precise evaluation and founding a sensible treatment strategy. On the other hand, since the presentation differs greatly among people, it often goes undiagnosed or can be easily misdiagnosed [27]. Though movement disorders were once thought to be associated with conventional antipsychotic medications, increasing attention is being given to the possibility of induction of movement disorders by most atypical

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antipsychotics [44]. On the other hand, some researchers believe that published prevalence rates of TD may be falsely low [45]. This is probably due to the insidious development of TD [46]. Back to our discussion and along with the findings of the current evaluation, the frequency of TD among our sample was lesser than what had been indicated by Koning et al. [4], Waln et al. [5], Kim et al. [6], Carbon et al. [7], Ward et al. [25], Saltz et al. [47], and Huang et al. [27], though it was slightly comparable to the finding of the last study [27]. Findings of Kim et al. [6], as well, were a bit comparable with the outcomes of the present assessment, though it was about atypical antipsychotic medications. On the other hand, maybe the presence of only male patients in the current estimation has altered the results adversely, which could be greater by the addition of female patients, especially when it has been declared that women are more likely to be affected than men [3,5].

Also, while the elderly schizophrenic patients shaped the present sample and increasing age is known as a risk factor for the development of TD [7], other similar studies are mostly about the prevalence of TD among adult patients aged between 20 and 70 [27]. Nevertheless, once more, the present outcome is remarkably less than the indicated measurements [3]. But, the present conclusion is somewhat similar to the findings of Go et al. [48], who found that patients of Filipino and Asian descent had a lower frequency of TD compared to patients of Caucasian descent, even though the Filipino and Asian patients consistently took a daily dose of 700 mg chlorpromazine for at least 5 years. By the way, while various factors like ethnicity, protective dietary factors and technical hitches may influence the outcome of prevalence studies, which have been conducted elsewhere in the world, currently no conclusive hypothesis may explain the existent variance. Moreover, in contrary to the findings of Huang et al. [27], in the present survey no significant relationship was clear between TD and dosage of antipsychotic medication, scores of negative symptoms, and severity of symptoms or age. But in the current survey, too, the occurrence of movement disorders in the facial and oral areas of chronic schizophrenic patients with TD was the most frequent finding [2,27]. This outcome is consistent with the earlier reports that the anomalous involuntary movements in head and facial zones, whose classic symptom is the mouth-tongue-cheek triple sign, are seen the most in patients with TD [49]. Also, in the existing appraisal, abnormal extremity movements were more prevalent than abnormal trunk movements, and the proportion of TD patients with multiple affected areas in comparison with TD patients with a single affected area was higher, outcomes which were comparable to the conclusions of Huang et al. [27].

But, the proportion of TD patients with self-awareness about their abnormal movements in the present assessment was remarkably higher than what has been recounted by Huang et al. [27]. Anyway, as said by some scholars, we do not have a deep understanding of this disorder due to its vague etiology, various clinical symptoms, many affected areas and wide variation in demonstration by patients [27]. So, the uncertain pathophysiology of TD remains to be a problem for the effective treatment of this ailment [40], particularly, by taking into consideration that TD may also occur in never-medicated patients with schizophrenia [3]. Accordingly, the best strategy against TD is prevention [40]. Therefore, healthcare staff are liable for teaching themselves and their patients about the risks associated with antipsychotic drugs and other TD-inducing prescriptions and following up the patients' compliance, and only allow patients to stay on these drugs for long periods if absolutely compulsory [40]. On the other hand, in many low- and middle-income countries there is also a lack of mental health resources, which results in a poorer ratio of medical staff to patients. In clinical practice, this may cause less time obtainable for each patient and hence a later recognition and diagnosis of TD [27]. Consequently, the APA has recommended monitoring patients with schizophrenia for the development of TD every

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3–12 months, depending on the patient's risk factors and the class of antipsychotic drug. Principles include every six months for patients on a typical antipsychotic drug to every twelve months for patients on an atypical antipsychotic medication [50]. Though implementation of the study in the senior group of schizophrenic patients could be accounted for as an advantage on behalf of the present valuation, small sample size, male gender, and lack of control group were among the weaknesses of the current appraisal, which could prevent generalization of the conclusion and thus confirm it as a pilot study. Further methodical studies in future with larger sample size may bring about more apposite results and will probably make the existing state of affairs brighter.

Conclusion

According to the finding of the present study, prevalence of Tardive Dyskinesia among elderly schizophrenic patients, who were using typical antipsychotic medications, is lower than what has been indicated thus far.

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Table 1: Medications that may induce or alleviate TD.

Medications That Can Induce TD	Medications and Supplements Used to Treat TD
Antipsychotic Drugs	Cholingergic Agents
Anticholinergic Agents	Clozapine, Quetiapine, Olanzapine
Antidepressants (Trazodone, doxepin, clomipramine, and amitriptyline, Fluoxetine, sertraline, Selegiline, Rasagiline, Phenelzine)	Apomorphine
Antiemetics	Vesicular monoamine transporter 2 (VMAT2) inhibitor
Anticonvulsants (Phenytoin carbamazepine and lamotrigine)	[Tetrabenazine, Tetrabenazine Analogs (Valbenazine and Deutetrabenazine)]
Antihistamines	Clonazepam.
Decongestants (Phenylpropanolamine)	Propranolol.
Antimalarials	Amantadine.
Antiparkinson Agents	Branched-Chain Amino Acids
Anxiolytics (Barbiturates, meprobamate benzodiazepines)	Ginkgo Biloba
Biogenic Amines (Tyramine)	Antioxidant Medications and Supplements (Zonisamide, yi gan san (a Chinese herb), levetiracetam, melatonin, omega-3 fatty acids, piracetam, resveratrol, vitamin B6, and vitamin E)
Mood Stabilizers (Lithium)	
Stimulants	

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Table 2: Comparative Analysis of Demographic and Psychopathologic Parameters.

Variables	Patients with TD (n=7)	Patients without TD (n=94)	T	P	CI
Age (y/o)	66.14±4.99	66.01±7.36	0.046	0.96	-5.50, 5.76
Duration of illness (years)	33.57± 3.06	31.79± 6.93	0.672	0.50	-3.47, 7.03
Mean (sd) mg/d Chlorpromazine equivalent	464.28±118.66	431.96±159.03	0.526	0.60	-89.64, 154.28
SAPS	63.71±9.62	57.44±10.16	1.580	0.11	-1.60, 14.14
SANS	55.38±6.40	49.96±8.37	1.674	0.09	-1.00, 11.84
SAI	7.61±2.97	8.83±3.11	1.004	0.31	-3.63, 1.19
CGI-S	4.10±2.35	3.22±1.16	1.776	0.07	-0.10, 1.86

Abbreviations: SAPS=Scale for Assessment of Positive Symptoms; SANS=Scale for Assessment of Negative Symptoms; SAI=Schedule for Assessment of Insight; CGI-S=Clinical Global Impressions–Severity of illness; TD=Tardive Dyskinesia

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