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360-Degree Impact of Tardive Dyskinesia: Functional, Emotional, and Social Impact

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Tardive dyskinesia (TD) is an involuntary movement disorder caused by prolonged exposure to dopamine receptor blocking agents (DRBAs) and is clinically defined by the delayed onset of persistent abnormal, involuntary, and repetitive (not rhythmic) movements.[1] Although TD emerges as a result of DRBA treatment, it has multiple repercussions besides being a serious—not transient—adverse effect, according to faculty members **Leslie Citrome, MD, MPH; Desiree M. Matthews, PMHNP-BC;** and **Henry Nasrallah, MD**. They maintain that TD is a neurological disorder that can adversely impact the whole patient. In this newsletter, they address the overall 360-degree impact of TD—in particular, its functional, emotional, and social impact—and discuss how they support the need for appropriate management.

Burden of TD Can Affect Many Patients Treated With DRBAs

Tardive dyskinesia is not rare; currently, an estimated 600,000 people in the United States are living with this movement disorder.[2,3] TD is associated with prolonged use of DRBAs used to treat a variety of neuropsychiatric disorders such as schizophrenia,[4] both phases of bipolar disorder, hallucinations/delusions,[5] and treatment-resistant major depressive disorder, among others. "Outside of psychiatry, DRBAs may be used to treat some gastrointestinal disorders," notes Dr Citrome, adding that package inserts warn of the risk for developing TD with longer-term use.[6] The expansion of the use of atypical antipsychotics beyond schizophrenia to the aforementioned conditions and off-label indications means that the number of people at risk for TD is likely to increase.[7]

To examine the risk for TD with exposure to first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs), Carbon and colleagues conducted 2 meta-analyses that were published in 2017 and 2018, respectively.[8,9] The first assessed 41 studies published since 2000 and reported exposure to FGAs and SGAs to be associated with an overall mean TD prevalence of 25.3% (range, 7%-30%; **Figure 1**).[8] The second meta-analysis, which examined data from 57 head-to-head randomized controlled trials including 32 FGA and 86 SGA arms, reported an annual TD incidence of 2.6% to 6.5%, with the higher values associated with FGAs.[9] They commented that these rates do not take into consideration disease severity or impact.[9]

"The reported lower rate of TD among people exposed to only SGAs may be an underestimate," comments Dr Citrome. "Cumulative exposure to antipsychotics is a major risk factor and, as people age, this risk continues to grow."

"Furthermore, patients at higher doses of SGAs are more vulnerable to TD than those receiving low doses, and patients with mood disorders and postmenopausal women are at higher risk for TD," adds Dr Nasrallah.

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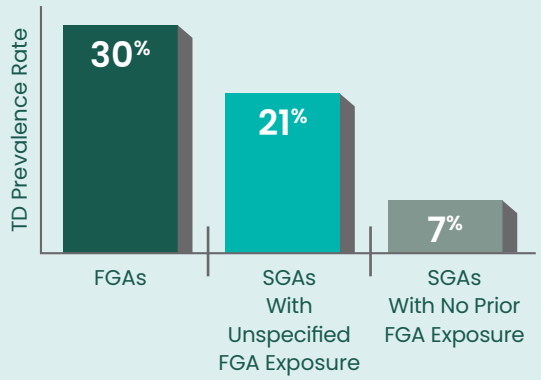
Figure 1. TD Prevalence[8]



N=11,493, meta-analysis including 41 studies that provided cross-sectional data from at least 15 FGA-, SGA-, or FGA + SGA-treated subjects and used a standardized rating scale to evaluate TD.

FGA, first-generation antipsychotic; SGA, second-generation antipsychotic. Based on: Carbon M, et al. *J Clin Psychiatry*. 2017;78(3):e264-e278.

"It is worth noting that there are patients living with TD who are not diagnosed accurately or are misdiagnosed as having a different movement disorder, such as acute extrapyramidal symptoms," notes Dr Nasrallah. Thus, published TD prevalence and incidence rates may be spuriously low.[10] TD and drug-induced parkinsonism both occur with typical and atypical antipsychotic use, and differentiating between these 2 conditions can be confusing.[10] However, it is important for clinicians to understand the differences between TD and drug-induced parkinsonism because the anticholinergic medications often used to treat drug-induced parkinsonism can worsen TD symptoms.[10]

TD Can Negatively Affect Patients' Overall Well-being

TD impacts more than muscle movements. It can negatively affect patients' quality of life, as reported in a cross-sectional web-based survey of patients with a clinician-confirmed diagnosis of bipolar disorder, major depressive disorder, or schizophrenia.[11] In this study, McEvoy and colleagues aimed to better understand the impact of TD on health-related quality of life (HRQoL) and social withdrawal among these individuals.[11]

When looking at all patients, regardless of underlying mental health condition, those with TD had significantly worse HRQoL.[11] In addition, decreases in HRQoL with increasing TD severity were mostly due to differences in responses to physical health-related questions on the SF-12v2, the patient-reported health survey used in the study.[11] These observations suggest that TD can negatively affect the physical health burden in patients who are also dealing with a preexisting mental health condition.[11]

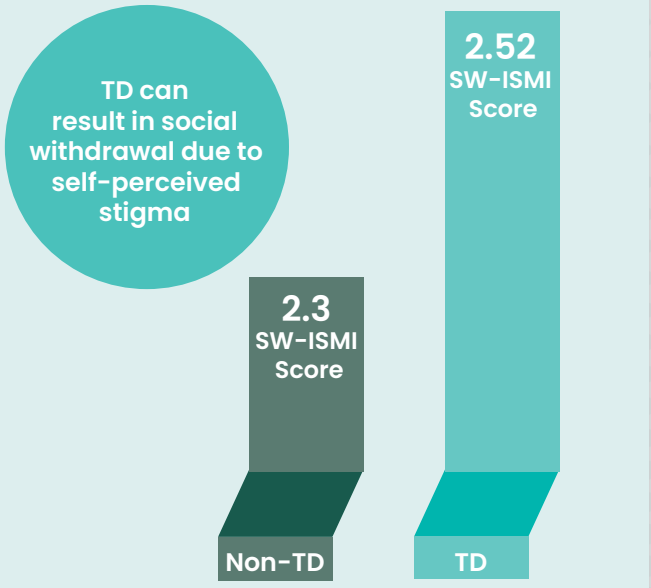
TD was also associated with worse scores in overall enjoyment and satisfaction, and was associated with increased social withdrawal.[11]

"It is truly unfortunate that patients with both serious psychotic and mood disorders, all of which can be disruptive to personal, vocational, and social functioning, can also have undiagnosed and untreated TD, which further impairs their quality of life," says Dr Nasrallah. "It is a sad example of adding insult to injury with 2 stigmatizing and damaging neuropsychiatric disorders."

Caroff and colleagues conducted a prospective study of the burden and impact of abnormal or unwanted movements designated by clinicians as probable or possible TD (n=204), using clinical observation and various assessments.[12] They found that more than three-fourths of patients with abnormal or unwanted movements consistent with TD have felt self-conscious or embarrassed about their symptoms.[12] Consistent with the findings of McEvoy and colleagues (**Figure 2**), Caroff et al reported that these feelings among patients with abnormal movements can exacerbate existing psychiatric symptoms and contribute to social isolation.[12]

"Not only do patients have to worry about how they are feeling mentally and emotionally, they may then have to battle with feeling they look different, worrying about the physical pain and limitations these uncontrolled movements can impose on themselves," says Ms Matthews.

Figure 2. Unwanted Movements May Contribute to Increased Social Isolation[11]



Cross-sectional web survey of patients with bipolar disorder, major depressive disorder, and schizophrenia, comparing social withdrawal in those with TD (n=197) and without TD (n=219) using the Social Withdrawal subscale of the Internalized Stigma of Mental Illness Scale (SW-ISMI).

Based on: McEvoy J, et al. *Qual Life Res*. 2019;28(12):3303-3312.

Patients additionally report that their TD can be disruptive, citing strength deficits in extremities and reduced steadiness of force control across various tasks,[13] as well as difficulty with chewing and swallowing.[14,15] TD can interfere with daily activities (eg, sleeping, leaving the house, eating/drinking) and can have negative effects on confidence, self-esteem, and self-worth.[16] "TD is not a cosmetic condition," says Dr Citrome. "It can interfere with a person's ability to eat, dress, or converse. It can lead to increased social isolation and further stigmatization." See boxed inset **Case Commentary: The Social Impact of TD** to hear some clinical practice anecdotes from the faculty.

Treating TD Is Not Difficult, But Has Been Challenging

"The first step in combatting TD is to acknowledge that it exists in your practice," says Dr Citrome. "The second step is to identify it. Once identified, management options can be discussed with the patient."

Despite the prevalence of TD, there is a long-standing, multidecade history of therapeutic nihilism, as FDA-approved treatments have only become available within the last few years.[17] Furthermore, the risk for TD is underestimated: prescribers might believe erroneously that not all patients treated with antipsychotic agents are at risk for TD, especially when SGAs are used,[18] or may not realize that TD is sometimes irreversible.[18] In addition, prescribers may not be aware of the many personal burdens associated with TD.[18]

Until the 2017 approval of vesicular monoamine transporter 2 (aka, VMAT2) inhibitors for the treatment of adult patients with TD,[17] the absence of an FDA-approved therapy was a barrier to treatment. Of note, off-label treatments for TD can have further negative consequences on the patient. Anticholinergic medications, which are indicated in the treatment of drug-induced parkinsonism, are not only ineffective but can, in fact, worsen TD symptoms in some instances.[19]

"Before there was treatment for TD, I was essentially blind to it. I was not actively looking for it because I could not offer patients any hope or meaningful way to reduce their movements associated with TD," says Ms Matthews. "But since the advent of FDA-approved treatments for TD, I am now much more vigilant and have my eyes and ears open."

"Historically, many psychiatrists believed that patients had to live with their abnormal movements, and they stopped evaluating it or even documenting it in patients' medical records," says Dr Nasrallah. "Now that evidence-based treatments have emerged for TD, some psychiatrists became early adopters and started recognizing and treating TD, but others continue to have a 'blind spot' about noticing TD movements, and therefore do not diagnose it or inform the patient about the new treatments that have become available, and actually administer them."

Case Commentary: The Social Impact of TD

"I have a patient, a 45-year-old man with major depressive disorder, who received treatment with an adjunctive atypical antipsychotic. He developed some minor tongue movements that were very noticeable to his wife, who would comment that it looked like he was chewing gum (he wasn't) and that he should just 'stop doing that' (he could not). The patient became very self-conscious about this and began to isolate himself from his friends and from colleagues at work. He was unaware that the movements were a consequence of his being on an antipsychotic and did not mention them to me. It went unnoticed by his care team until I met with his family and his wife was listing all the things that he does that 'drive her crazy.'"

– Leslie Citrome, MD, MPH

"Patients have varying concerns with the burden of TD—anywhere from physical pain to social embarrassment. I had one patient who had been exposed to multiple antipsychotics for bipolar I disorder. He developed uncontrolled movements from TD, with multiple areas involved (face, hands/wrists, toes/ankles). He reported that his toenail ended up falling off due to the constant friction from the uncontrolled movements of his toes rubbing up against the work boots he had to wear for long hours at his construction job. This caused him significant pain and discomfort and difficulty ambulating and working without pain."

– Desiree M. Matthews, PMHNP-BC

"One of my patients, who was recovering from bipolar disorder but developed facial and upper extremity TD movements, had to drop out from group therapy (which she enjoyed) because other patients stared at her most of the time and commented about how her movements were distracting them from the group discussions. The patient was very disheartened and hopeless."

– Henry Nasrallah, MD

Conclusion

Although TD is an iatrogenic disorder that emerges as a result of DRBA treatment, it is not simply a transient side effect. An estimated 600,000 people in the United States are diagnosed with TD, and that number is expected to rise with the expanding use of antipsychotics for various conditions. TD can affect so much more than movement; patients report that they are frustrated and embarrassed by their TD, and that their overall physical and social function, quality of life, and well-being can suffer as a result. Although FDA-approved treatments are available, barriers persist, including therapeutic nihilism and a lack of awareness of TD incidence and impact.

References

1. Aquino CC, Lang AE. Tardive dyskinesia syndromes: current concepts. *Parkinsonism Relat Disord*. 2014;20(suppl 1):S113-S117.
2. Robert L. Tardive dyskinesia facts and figures. *Psychiatric Times*. May 30, 2019. Accessed November 23, 2020. https://www.psychiatrictimes.com/tardive-dyskinesia/tardive-dyskinesia-facts-and-figures
3. Cloud LJ, Zutshi D, Factor SA. Tardive dyskinesia: therapeutic options for an increasingly common disorder. *Neurotherapeutics*. 2014;11(1):166-176.
4. Loughlin AM, Lin N, Abler V, et al. Tardive dyskinesia among patients using antipsychotic medications in customary clinical care in the United States. *PLoS ONE*. 2019;14(6):e0216044.
5. Yohanna D, Cifu AS. Antipsychotics to treat agitation or psychosis in patients with dementia. *JAMA*. 2017;318(11):1057-1058.
6. Chlorpromazine [package insert]. Amneal Pharmaceuticals, LLC; 2019.
7. Caroff SN, Citrome L, Meyer J, et al. A modified Delphi consensus study of the screening, diagnosis, and treatment of tardive dyskinesia. *J Clin Psychiatry*. 2020;81(2):e1-e22.
8. Carbon M, Hsieh CH, Kane JM, Correll CU. Tardive dyskinesia prevalence in the period of second-generation use: a meta-analysis. *J Clin Psychiatry*. 2017;78(3):e264-e278.
9. Carbon M, Kane JM, Leucht S, Correll CU. Tardive dyskinesia risk with first- and second-generation antipsychotics in comparative randomized controlled trials: a meta-analysis. *World Psychiatry*. 2018;17(3):330-340.
10. Ward MW, Citrome L. Antipsychotic-related movement disorders: drug-induced parkinsonism vs. tardive dyskinesia—key differences in pathophysiology and clinical management. *Neurol Ther*. 2018;7(2):233-248.
11. McEvoy J, Gandhi SK, Rizio AA, et al. Effect of tardive dyskinesia on quality of life in patients with bipolar disorder, major depressive disorder, and schizophrenia. *Qual Life Res*. 2019;28(12):3303-3312.
12. Caroff SN, Yeomans K, Lenderking WR, et al. RE-KINECT: A prospective study of the presence and healthcare burden of tardive dyskinesia in clinical practice settings. *J Clin Psychopharmacol*. 2020;40(3):259-268.
13. Vrtunski PB, Alphs LD, Meltzer HY. Isometric force control in schizophrenic patients with tardive dyskinesia. *Psychiatry Res*. 1991;37(1):57-72.
14. Gregory RP, Smith PT, Rudge P. Tardive dyskinesia presenting as severe dysphagia. *J Neurol Neurosurg Psychiatry*. 1992;55(12):1203-1204.
15. Bhat PS, Pardal PK, Diwakar M. Dysphagia due to tardive dyskinesia. *Ind Psychiatry J*. 2010;19(2):134-135.
16. Data on file. Neurocrine Biosciences, Inc.
17. U.S. Food and Drug Administration. FDA approves first drug to treat tardive dyskinesia. April 11, 2017. Accessed November 23, 2020. https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-treat-tardive-dyskinesia
18. Caroff SN, Ungvari GS, Owens DGC. Historical perspectives on tardive dyskinesia. *J Neurol Science*. 2018;389:4-9.
19. Bergman H, Soares-Weiser K. Anticholinergic medication for antipsychotic-induced tardive dyskinesia. *Cochrane Database Syst Rev*. 2018;1(1):CD000204. doi: 10.1002/14651858.CD000204.pub2.

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