Tardive Dyskinesia in Older Persons Taking Antipsychotics

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Abstract: Tardive dyskinesia (TD) is a hyperkinetic movement disorder caused by the use of dopamine receptor-blocking agents (DRBAs), a category of medications that includes first- and second-generation antipsychotics (APs) and agents such as metoclopramide that are used for the treatment of nausea and gastrointestinal dysmotility. While TD can affect people of all ages, older age is associated with increased risk of TD and also with the emergence of TD occurring after shorter treatment durations and lower dosages of DRBAs. TD is characterized by involuntary movements that include the face, limbs, and trunk, and is associated with increased comorbidities, social stigmatization, and impaired physical and mental health. Once present, TD tends to persist despite AP dose adjustment or discontinuation. Even with the use of US Food and Drug Administration (FDA)-approved medications for TD, symptoms may persist. Because the leading hypothesis for the pathophysiology of TD has been dysregulation of dopamine transmission due to treatment with DRBAs, APs that avoid postsynaptic dopamine receptor blockade may provide an alternative therapeutic approach for patients who require an AP. In this review, we discuss the risks, burdens, prevention, and management of TD, with a focus on older people.

Keywords: tardive dyskinesia, antipsychotic medications, age

Introduction

Tardive dyskinesia (TD) is a hyperkinetic movement disorder caused by dopamine receptor-blocking agents (DRBAs), a category of medications that includes antipsychotics (APs) and some agents used to treat nausea and gastrointestinal dysmotility, such as metoclopramide.[1] The Diagnostic and Statistical Manual of Mental Disorders, 5th edition, defines TD as involuntary athetoid or choreiform movements. Symptoms must last for at least a few weeks and develop in association with the use of a neuroleptic medication for at least a few months.[2] TD is often irreversible, can impact daily life, and can be socially stigmatizing.[3] While all individuals treated with DRBAs are at risk for developing TD, older individuals are at higher risk and particularly vulnerable to developing this disorder, even after shorter exposure to newer second-generation APs.[4–7]

In addition to their US Food and Drug Administration (FDA)-approved indications, APs have also been used for non-approved (ie, "off-label") indications,[7] including neuropsychiatric symptoms associated with Parkinson's disease or dementia. The increasing and widespread use of APs has led to more elderly people being placed at risk of TD.[8–11] Moreover, older individuals on APs may face a greater risk for complications related to TD, as they are more prone to falls, orthostatic hypotension, somnolence, and generally have a greater burden of

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comorbidities than younger people.[12–16] The aim of this review is to examine the risk, burden, and management of TD with a particular focus on the elderly.

Overview of Tardive Dyskinesia

TD is characterized by a delayed onset of involuntary motor movements in the face, trunk, and limbs after exposure to DRBAs.[4,17] Involuntary movement are classically peri-oral, including grimacing, tongue protrusion, and lip puckering, but also include neck, shoulder, and limb movements.[18] In some cases, symptoms can be severe enough to interfere with breathing, speaking, eating, and ambulation.[19,20]

TD is often irreversible and can impose long-lasting burdens on psychosocial, physical, and economic health.[4,21–23] Historically, assumptions that those afflicted are unaware of their symptoms or unconcerned with them have obscured these burdens, especially among persons with schizophrenia who can have limited insight into their physical and mental health.[24,25] However, a recent study of those with a history of AP use for the treatment of schizophrenia, schizoaffective disorder, mood disorder, and other psychiatric disorders, found that nearly 80% of subjects with a clinician-confirmed diagnosis of possible TD reported noticing recent involuntary movements.[21] Many of these individuals also felt that the uncontrollable movements impacted their ability to engage in daily activities, talk, or socialize.[21]

The degree to which those with TD experience reduced general health, life enjoyment and satisfaction, and enhanced social withdrawal is generally proportional to the severity of the symptoms.[3] The disorder can impact leisure activities or the willingness to participate in community activities. TD can also hinder the ability to find and maintain employment due to the symptoms themselves or embarrassment caused by the symptoms.[21,26] The financial impact of TD on the healthcare system can be considerable, as reported in a large, retrospective analysis that found that people with both TD and schizophrenia, mood disorders, or other psychiatric disorders experience 29% more hospital admissions, 5% more outpatient visits, and 21% more emergency room visits than those without TD.[22] This results in a nearly doubling of the healthcare-related financial burden for individuals with TD from $28,777 to $54,656 over a 2-year period.[22]

Prevalence and Risk of TD

The mean prevalence of TD in people treated with APs was 20–25% according to meta-analyses of articles published between 1959 and 2015.[27,28] A 20-year longitudinal study initiated prior to the widespread use of second-generation APs calculated a yearly cumulative incidence of TD of 4%–5%.[27] The frequent occurrence of TD and acute extrapyramidal symptoms, such as drug-induced parkinsonism and acute dystonia, encouraged the development of second-generation APs, which were intended to minimize the incidence of adverse neurological effects. Although acute drug-induced parkinsonism and acute dystonia are lessened, TD has not been eliminated. The annual prevalence of TD among patients receiving APs was estimated to be 7.6 to 9.7 per 1000 people according to a large retrospective observational study of electronic health records, with nearly 80% of study participants using second-generation APs.[15] A direct comparison of annualized incidence between first- and second-generation APs indicates a reduced but not eliminated risk of TD with use of second-generation APs (range of 0.8% to 3% with use of second-generation APs vs 5.4% to 7.7% with use of first-generation APs).[6,29]

The most important risk factors for the development of TD include older age and cumulative exposure to the DRBA. Other risk factors include the dopamine-receptor binding affinity of the DRBA in question, female sex, mood disorders, dementia, and prior drug-induced parkinsonism.[4,30–33] Smoking and substance abuse may also be associated with a higher risk of developing TD.[33]

TD in Older Populations

As noted, age is a key risk factor for developing TD.[31,34] A study of 404 people aged ≥55 years reported cumulative TD incidences of 26%, 30%, and 60% after the first, second, and third year, respectively, of first-generation AP use.[35] This is considerably higher than that observed in younger people; a meta-analysis of 32 randomized studies that included 10,706 subjects of mixed ages calculated an annualized TD incidence of 6.5% with the use of first-generation APs.[28] Second-generation APs offer older people a reduced risk of approximately 6% and 7% after the first year of use to 11% after the second year of use in those who are naïve to first-generation APs. However, the risk (nonetheless remains higher than the incidence of ≤3% observed among younger adults treated with second-generation APs.[29,36] Although TD risk increases in a dose-dependent manner, older patients are susceptible after exposure to even low doses of second-generation APs.[4,37] A study of 255 older patients with dementia (mean age: 82.5 years) found that 1.7% of patients treated daily with 0.75 to 1.5 mg risperidone for 1 year developed TD; in contrast, no new cases of TD were reported

in a mixed-age adult population of 541 patients treated with a mean dose of risperidone 3.9 mg/day for 6 months.[37,38] Similarly, no change from baseline was observed in TD symptoms among adults aged ≤65 years after 1 year of 4 to 10 mg risperidone daily.[39] The mechanism underlying age-related increased susceptibility is unclear but may be due to higher cumulative exposure to APs as well as an age-related decrease in dopaminergic neurons in the substantia nigra.[40]

Because APs are sometimes used off-label for dementia-related psychosis and aggression,[8,11] TD can be encountered in this population, particularly within facilities that care for older people. Up to 33% of patients residing in nursing homes or assisted living facilities receive APs, predominantly for off-label indications.[8] A survey of 350,000 nursing home residents in 8 states, representing 40% of residents nationally, found that in 2006, 27.6% of residents had taken APs in the last 7 days, and only 20.7% of these were for treatment of the primary indications of schizophrenia or bipolar disorder.[41] The National Nursing Home Survey of 300,000 residents found that 23% of respondents had received at least 1 second-generation AP, and 86.3% of these prescriptions were for off-label indications.[42] Dementia is one of the most common indications for off-label AP use in these facilities, despite the bolded "black box" warning against AP use in patients with dementia-related psychosis.[8,11] Behavioral issues related to dementia may in part drive AP use in this population. Crystal et al found that half of residents with dementia and aggressive behavior received AP treatment, while 40% and 23% of patients with non-aggressive dementia or dementia without behavioral symptoms, respectively, also received APs.[41] Other common reasons for off-label AP use among older people are anxiety and insomnia.[8] The prevalence of off-label AP use, particularly among older individuals, has prompted the Centers for Medicare and Medicaid Services to issue guidelines and fact sheets recommending against this practice,[43] and long-term care settings are compelled to adhere to efforts to mitigate their use. However, recent studies suggest AP use outside of approved indications continues.[44,45]

Impact of TD in Older People

The impact of TD on an individual's physical, mental, and economic health may intensify with age.[3,22] The social and emotional effects of symptoms are highly debilitating for people with TD of all ages, but feelings of isolation and depression may be especially profound for older

people.[3,16] Older individuals are also uniquely vulnerable to the physical consequences of TD, such as impaired gait and balance, which can lead to falls.[16,26] TD in older patients often presents as oro-bucco-lingual dyskinesia, and these movements can interfere with eating and swallowing; incidents of choking resulting from respiratory TD have been reported.[7,19,46] Further, oro-bucco-lingual TD can cause loosening of natural and artificial teeth and be augmented by edentulousness and denture use; edentulousness itself can cause abnormal movements of the mouth in the absence of neurological disorders such as TD.[26,46,47] Older patients may also be affected by dyskinesias of the limbs, trunk, and respiratory system, with symptoms such as grunting.[7,26,48]

The observation that older people with TD are also at increased risk of cardiac, metabolic, and other movement disorder comorbidities complicates treatment of TD in these patients.[12–15] Lastly, the high healthcare utilization costs associated with TD are likely to severely tax the resources of older people on fixed or limited incomes and stress the healthcare system in general.[22] Given these considerable impacts, treatment plans for older individuals with psychiatric conditions should include modification of prescribing practices to minimize the risk of TD.

Mechanisms of TD with APs

Understanding the pathophysiology of TD is essential to choosing therapies for psychiatric conditions that minimize the risk of this disorder in older patients. While there is not a universally accepted mechanism through which APs drive the development of TD, a leading hypothesis revolves around the dysregulation of dopaminergic transmission.[49,50] Antagonism of postsynaptic dopamine D2 receptors in the mesolimbic pathway, specifically in the ventral striatum, drives efficacy of APs in reducing positive symptoms associated with psychosis. However, long-term blockade of D2 receptors in the nigrostriatal pathway, specifically in the dorsal striatum, can lead to an increase in the number and function of postsynaptic dopamine D2 receptors (often referred to as the "supersensitivity" or "hypersensitivity" hypothesis) subsequently interfering with voluntary motor control.[4,51,52] This enhanced sensitivity to dopamine in the dorsal striatum can lead to several types of motor symptoms, including TD. Genetic studies in support of a role for dopamine hypersensitivity in TD include observations that mutations in the *PIP5K2A* and *DRD2* dopamine receptor genes and in the glycine variant of the

dopamine D3 receptor have been linked to the development of TD in people with schizophrenia.[53–55]

Second-generation APs are thought to carry a lower risk for the development of TD compared with first-generation APs because although both types of APs are DRBAs, second-generation APs are also antagonists at presynaptic serotonin 5-HT$_{2A}$ receptors, which can lessen the risk of drug-induced movement disorders in general. In addition, some second-generation APs have a lower binding affinity to the postsynaptic dopamine receptor as well.[18,56,57]

Investigational uses of functional magnetic resonance imaging (fMRI) to help elucidate the pathophysiology of TD are also of interest. For example, two recent reports demonstrated statistically significant differences in gray matter volume and resting state functional connectivity of motor-related brain regions of interest in patients with schizophrenia treated with antipsychotics with and without a TD diagnosis. Gray matter volumes of the brainstem, inferior frontal and precentral gyri, cuneus, and lingual gyrus were significantly different in patients with TD than in those without.[58] Similarly, patients with TD exhibited a reduction in resting state functional connectivity between the right postcentral gyrus and the inferior frontal gyrus of the left triangular part compared with patients without TD.[59] Gray matter volumes of the cuneus and lingual gyrus and the reduction in resting state functional connectivity observed were also correlated with TD severity, as assessed by the total score on the Abnormal Involuntary Movement Scale, providing further support that changes in gray matter volume or functional connectivity may be related to the pathophysiology of TD.[58,59] The use of fMRI in evaluating TD remains investigational, and its relevance in older populations deserves further study.

Strategies for Minimizing TD Risk

TD can be irreversible, highlighting the need for preventative strategies. Many clinicians focus primarily on limiting the use of TD-inducing medications and secondarily on detecting TD symptoms early.[51,60,61] Considering the pharmacology of individual APs with an understanding of proposed TD pathophysiology informs the selection of therapies that are least likely to induce TD. Use of less potent dopamine receptor blocking second-generation APs instead of first-generation APs may reduce TD risk. Correll and colleagues presented the initial support for a lower risk of TD associated with second-generation APs compared with first-generation APs in a meta-analysis of 11 randomized studies.[6] Here, the annual TD risk estimate associated with haloperidol was 5.4%

across 3 studies, whereas across 5 studies, the risk estimates associated with olanzapine, risperidone, quetiapine, or amisulpride ranged from 0.5% to 1.5%. In addition, because older people both experience benefit from second-generation APs at low doses and are at greater risk of developing TD after minimal exposure, treatment regimens should reflect these sensitivities and implement the lowest effective AP dose.[7,62]

Several nondopaminergic approaches to treat psychosis are also in development. Serotonin receptor inhibition has not been associated with TD, and selective inverse agonism/antagonism of 5HT receptors may be a therapeutic strategy that would mitigate the risk of TD.[63] Another potential preventative strategy is treatment of psychiatric disorders through selective agonism of the trace amine-associated receptor 1 (TAAR1), an approach that has recently been shown to improve symptoms of schizophrenia in adults and does not induce motor abnormalities in animal models.[64] Targeting the muscarinic system with a combination of xanomeline and trospium has also been proposed as a nondopaminergic strategy for mitigating TD risk.[65,66]

Current Therapeutic Strategies for TD in Older Patients

The first step in developing the optimal treatment strategy for TD is timely diagnosis, which requires the clinician to be routinely vigilant.[67] Diagnosis is based on history of exposure to DRBAs, and a minimum duration of only 1 month of AP exposure is required to diagnose TD in individuals aged ≥60 years, compared with 3 months in younger adults.[2,7,60]

An early strategy to mitigate TD symptoms involves modification of the existing AP medication regimen if clinically feasible.[68] However, success with this approach is often limited.[23,68,69] Two vesicular monoamine transporter 2 (VMAT2) inhibitors, valbenazine and deutetrabenazine, have been approved by the US FDA to treat TD.[68,70,71] Recent guidelines for the treatment of schizophrenia recommend VMAT2 inhibitors as first-line therapy for patients who have moderate to severe or disabling TD or for patients with mild TD on the basis of such factors as patient preference, associated impairment, or effect on psychosocial functioning.[72] In two recent studies of subjects aged ≥55 years who had participated in clinical trials conducted by the manufacturer, Sajatovic et al demonstrated that valbenazine (median: 61 years, range: 55–84 years) and

deutetrabenazine (mean age: 63.1 years, range: 55–81 years are well tolerated in older individuals.[73,74] Of note, VMAT2 inhibition manages the symptoms of TD but does not cure them; dyskinetic movements generally return when the VMAT2 inhibitor is discontinued.[75]

Although anticholinergic agents may effectively treat acute drug-induced parkinsonism, these medications can worsen TD.[23] Anticholinergic drug burden is also associated with impaired cognition. Discontinuation of anticholinergic medication leads to an improvement of TD symptoms in approximately 60% of people, and if enacted, should be done gradually.[23,76] An additional benefit from deprescribing anticholinergic medication would be a lessening of the memory impairment and other anticholinergic adverse effects associated with this class of drug.[77]

Avoiding TD by eliminating exposure to DRBAs may be the best option for older persons. Several novel agents are being studied for their antipsychotic properties. Alternative mechanisms, including serotonin inverse agonism/antagonism in the absence of dopamine receptor blockade, agonism of TAAR1 receptors, and modulation of muscarinic cholinergic receptors, may provide different therapeutic approaches for patients who require a medication with an AP effect and avoid contributing to the risk of developing TD.[63–66]

Conclusion

TD is a particular concern for elderly individuals treated with DRBAs, including second-generation APs. The prevalence of TD in this population is up to 5 to 6 times that of younger people and is encountered clinically in part because of the off-label prescription of APs for dementia-related behavioral and psychological disorders.[7,11] In addition to the TD symptoms themselves, older people may be more severely impacted by associated comorbidities and impaired physical and mental health.[13–15,78]

Although the recent approval of VMAT2 inhibitors provides a new therapeutic option once TD occurs, avoiding this often irreversible movement disorder would be preferred. An important strategy for mitigating TD risk is prescribing APs that address psychiatric conditions while minimizing the risk of developing this disorder. Currently, second-generation APs are recommended over first-generation APs.[23] However, the risk of TD among older individuals persists at a rate of approximately 6% with use of second-generation APs.[36] Newer APs that are effective in treating mental health disorders but that do not block postsynaptic dopamine D2

receptors in the dorsal striatum, and thus do not carry a significant risk for TD, are needed.

Abbreviations

APs, antipsychotics; DRBAs, dopamine receptor-blocking agents; FDA, Food and Drug Administration; TD, tardive dyskinesia; VMAT2, vesicular monoamine transporter 2.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

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