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Tardive dyskinesia: Who gets it and why

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ABSTRACT

Tardive dyskinesia (TD) is a potentially permanent movement disorder resulting from chronic use of dopamine receptor blocking agents (DRBA). Identified risk factors include the type of antipsychotic agent, being greater for those of first generation antipsychotics (FGA), the duration of illness and cumulative dose of DRBA and advanced age. Female sex and African and Caucasian ethnicity are additional potential risk factors. Because only a subset of people taking DRBA's develops TD, genetics may play a role. Susceptibility gene candidates include those involved in DRBA metabolism and the targets or receptors of DRBA's. Although met with conflicting data, the following genes may be involved with TD development: the cytochrome P450 gene CYP2D6, involved with metabolism of most antipsychotics, Dopamine D2 and D3 receptor genes, serotonin 2A and 2C receptor genes, vesicular monoamine transporter 2 (VMAT 2) gene, involved with intracellular neurotransmitter packaging, and the manganese superoxide dismutase (MnSOD) gene, an antioxidant enzyme. Heparan sulfate proteoglycan 2 (HSPG 2) gene is another potential gene involved with development of TD. The pathogenesis of TD is unknown, however there are three main theories proposed: dopamine receptor supersensitivity resulting from chronic dopamine receptor blockade, oxidative stress and maladaptive synaptic plasticity each of which is discussed further in this article.

Tardive dyskinesia (TD) is a potentially permanent and disabling adverse effect from certain medications. By definition TD is the insidious onset of rhythmic, repetitive, stereotypic movements of the face, mouth and tongue, often with involvement of the trunk and extremities that occur as a result of dopamine receptor blocking agents (DRBA) [1]. The term tardive refers to the delayed onset of the disorder. The mean prevalence of TD is estimated to be 25.3% in psychiatric patients taking antipsychotics [2]. Compared to the number of people taking these drugs, TD represents a minority. TD is a potentially permanent condition; stopping the offending agent does not always alleviate the condition. Therefore, prevention of TD by avoiding DRBA's if at all possible is ideal. However, there is no apparent way to predict who will develop TD and there are some cases in which DRBA's are necessary for treatment of chronic conditions. As TD has been present since the development of DRBA's, possible risk factors for its development have been studied. Solmi et al. (2018) [3] have written a comprehensive review on this subject.

1. Risk factors for TD

Many risk factors have been researched and they can be divided into two classes: modifiable risk factors and nonmodifiable risk factors. The main modifiable risk factors include type of DRBA, duration of illness, dosage and length of time of exposure to the DRBA [2–8]. Additional potential modifiable risk factors include diabetes, smoking, alcohol and cocaine abuse/dependence, akathisia, intermittent antipsychotic treatment and anticholinergic treatment [3]. The major nonmodifiable risk factor is advanced age [3,8–12]. Female sex, Caucasian or African ethnicity are potential nonmodifiable risk factors [2,3,7,14]. Genetic variation or susceptibility may mediate risk for TD development. Additional less studied, potential nonmodifiable risk factors include intellectual disability, brain damage, negative symptoms in schizophrenia, mood disorders and cognitive symptoms [3].

TD commonly results from the use of antipsychotics but has also been seen with other types of medications. Gastrointestinal medications such as prochlorperazine, is an example of a nonantipsychotic DRBA reported to cause TD. Additionally, antidepressants which are not DRBA's have been known to produce TD through unknown mechanisms. Rarely, calcium channel blockers have been found to result in TD (See Table 1 for a list of main drugs that can cause TD).

There are differences between the types of antipsychotics with respect to TD development. First generation antipsychotics (FGA), such as haloperidol, tend to carry a greater risk for development of TD compared to second generation antipsychotics (SGA), such as risperidone. It

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Table 1
Main Drugs that can cause Tardive Dyskinesia.

Class of Drug	Examples of Drugs causing Tardive Dyskinesia
First Generation Antipsychotic	Haloperidol, Chlorpromazine, Thioridazine, Thiothixine, Pimozide, Perphenazine,Trifluoperazine
Second Generation Antipsychotic	Risperidone, Paliperidone, Iloperidone, Loxapine, Olanzapine, Aripiprazole, Ziprasidone, Asenapine, Lurasidone, Quetiapine, Clozapine
Antiemetic	Metoclopramide, prochlorperazine
Antidepressants	Trazodone, Amitriptyline, Clomipramine, Amoxapine, Fluoxetine, Sertraline
Calcium Channel Blockers (rare)	Cinnarizine, Flunarizine

is thought that the difference may be due to degree of dopamine receptor blockade. FGA's tend to have 85% occupancy while SGA's tend to have from 35 to 75% occupancy of the D2 dopamine receptors [4]. Comparing patients with and without TD in the CATIE study (Clinical Antipsychotic Trials of Intervention Effectiveness) those with TD tended to be taking FGA's [5]. A meta-analysis looking at 41 studies of patients with various psychiatric disorders treated with antipsychotics showed TD prevalence to be 30.0% with FGA and 20.7% with SGA use [2] and a longitudinal study of outpatients with psychiatric disorders maintained on antipsychotics with four year follow up of 352 patients showed a cumulative incidence of TD 44.9% with FGA and 24.1% with SGA use at six months [6].

Higher dosage, longer duration of illness and greater length of time of exposure to the DRBA, in other words, larger cumulative doses of DRBA, have been associated with a greater risk of TD [2,5,7,8]. There is no safe dose of DRBA. TD has been reported to occur within a short period of time as well as many years after initiating treatment with DRBA's. There have been case reports of TD occurring with less than 1 month of DRBA exposure the earliest being 17 days of exposure [10]. In a study of TD in the elderly, Jeste et al. (1999) reported TD beginning within one month of taking neuroleptics [13] The DSM IV criteria was based on Schooler and Kane's criteria for the diagnosis of TD for research purposes. A minimum of 3 months of DRBA exposure in those younger than 60 years is required for the diagnosis of TD [11,14].

Advanced age is a well-recognized risk factor for the development of TD. Nearly every study on the incidence of TD has found increasing age to be a risk factor for TD. With a mean age of 66.2 years the one month incidence of TD was 3.4%, 3 months 5.9% and 1 year 23% [9]. An older study of patients with a mean age of 65.5 years showed the prevalence of TD to be 26.1% at one year 51.7% at two years and 59.8% at three years [8]. Similar to previous studies, the prevalence of TD in the elderly was found to differ between the types of antipsychotic used. A meta-analysis of 23 papers found the prevalence to be 23% with FGA and 7% with SGA at one year in patients over 50 years of age [12]. It is thought that the risk for patients over 60 years of age is three times that of younger patients and that the development of TD may occur much sooner in this patient population. The incidence of TD was 5.9% at 3 months in a population over 45 years of age [13] whereas younger patients have a 4–5% incidence at about one year of exposure to neuroleptics. The earlier development of TD in the elderly has been reflected by the DSM IV criteria for TD requiring only one month of DRBA use for those over 60 years of age compared to three months for younger patients [14]. It is thought that older patients require lower doses compared to younger patients due to differences in drug distribution, reduced metabolism and excretion [15].

It has long been thought that female sex is another risk factor for development of TD. Yassa and Jeste (1992) [16] reviewed 76 articles on the prevalence of TD up to 1989. They found a significant difference in gender with 21.6% men and 26.6% women taking neuroleptics having TD. However, this gender difference has not been found by other studies [5,7]. Van Os et al. (1999) [17] did not find a difference with respect to gender in their study of 690 patients with psychosis in the UK. Additionally, a more recent meta-analysis did not find any difference with respect to gender in the prevalence of TD [2].

Race and ethnicity have also been thought to represent potential risk factors for the development of TD; however studies have shown conflicting results. African ethnicity has been reported to have about twice the risk of TD compared to Caucasians [7]. However, Caucasian race was found to have an increased risk for TD development in a meta-analysis [2] and no difference between races was found in the CATIE trial [5].

Prevention of TD is the goal and avoidance of DRBA's if at all possible is recommended, especially in patients over 60 years of age. In those cases requiring chronic DRBA treatment, the use of SGA's is preferred over FGA's. Monitoring patients taking FGA's every six months and SGA's every year for TD is recommended [3].

1.1. Genetics

There is a hypothesis that TD is a pharmacogenetic disease, developing due to the interaction between DRBA exposure and individual genetic variation [29]. Because only a minority of people taking DRBA's develops TD, genetic susceptibility may play a role in its development. It is possible that inheritance of a susceptibility gene under the right circumstances can result in the development of TD. Two types of genes have been studied with regards to TD: genes involved in the metabolism of DRBA's and genes linked to the targets or receptors of the drugs [18].

The liver enzyme cytochrome P450 family 2 subfamily D member 6 (CYP2D6) is involved in the metabolism of most antipsychotic drugs. An animal model of TD in which chronic treatment with haloperidol induces vacuous chewing movements in rats found an increase in the movements with CYP2D inhibition [19] implicating its role in protection from TD. The CYP2D6 gene is located on chromosome 22q13.2, is polymorphic with over 100 known allelic variations and has four different phenotypes with respect to CYP2D6 metabolism status. Poor metabolizers have two null alleles, intermediate metabolizers have one reduced and one null allele or two reduced activity alleles, extensive metabolizers have one functional allele and ultrarapid metabolizers have multiple functioning alleles [20]. It is thought that poor metabolizers are at greater risk of developing TD by producing a greater cumulative drug dosage. There are conflicting results from studies, however. Koola et al. (2014) [20] found an increase in TD associated with a greater ability to metabolize CYP2D6 in their study population of 70 schizophrenic patients. They hypothesized a toxic metabolite which accumulates more in ultrarapid metabolizers may be responsible for their results. A meta-analysis of twelve studies looking at the development of TD in schizophrenic patients and CYP2D6 metabolizer status showed possession of loss of function alleles (poor and intermediate metabolizers) may increase the risk of development of TD [21]. Another factor which may influence these study results is the differential metabolism of the different antipsychotics used. Additional cytochrome P450 enzymes such as CYP1A2 and CYP3A5, which are also involved in the metabolism of some antipsychotics, have not been as extensively studied with respect to their involvement as a risk factor for TD. More comprehensive studies with greater numbers of patients are needed before a conclusion can be made.

Both the dopamine D2 (DRD2) and D3 (DRD3) receptor genes have been proposed to be involved in the development of TD. DRD2 is the main target for antipsychotic drug action. It is possible that genetic variants in the DRD2 gene may predispose towards the development of TD. However, results from studies of the DRD2 gene appear to be conflicting. Of the possible DRD2 gene alleles studied, Taq1A seems to

be the most promising candidate with respect to TD. A meta-analysis of 12 studies also found this allele to be associated with TD [22].

DRD3 is one of the more studied genes with respect to risk of TD. The ser-9-gly polymorphism which results in greater binding affinity for dopamine has been thought to produce a differential susceptibility for the development of TD and has been found to be associated with TD in those treated with FGA's. Study results have been inconsistent, however. A meta-analysis of 11 studies showed an association between the ser-9-gly polymorphism and TD [23]. Conversely, a more recent meta-analysis of 13 studies did not show such an association [24]. With the promising study results, a commercial test for this polymorphism has been produced in hopes of identifying at risk populations in an effort to prevent TD thus introducing additional ethical considerations [25].

Serotonin is thought to regulate release of dopamine and both the serotonin 2A and 2C receptors have been studied as possible candidate genes for TD. Clozapine binds to the 2A receptor and confers a lower risk for development of TD. Several studies have found an association between the common polymorphisms T102C and A1438G of the serotonin 2A receptor gene and TD. The homozygote condition tended to be associated with greater severity of TD inferring differential clinical effects of this gene [26]. This result has not been confirmed, however and Basile et al. (2001) [27] did not find an association between the serotonin 2A receptor gene and TD in their population of 136 schizophrenic patients. Further study of this gene is warranted.

Serotonin 2C receptor antagonism has been found to reduce vacuous chewing movements in chronic haloperidol treated rats [28]. Few studies have been performed and results have been contradictory.

Vesicular Monoamine Transporter 2 (VMAT 2) is involved with the packaging of neurotransmitters such as dopamine into vesicles in the cellular cytoplasm. Tetrabenazine and its derivatives are selective VMAT 2 inhibitors useful in the treatment of TD. Mutations of the VMAT 2 gene (also known as the solute carrier family 18 member A2 or SLC18A2) may be involved in TD development. Tsai et al. (2010) found an association between SLC18A2/rs2015586 allele and TD in their population of 207 schizophrenic patients with TD involved in the CATIE trial [29]. In addition Zai et al. (2013) reported an association between the SLC18A2/rs2015586 allele as well as the rs36224A allele in their population of 217 schizophrenic patients with TD. The rs36224 AA genotype was thought to be protective against TD [30].

Manganese superoxide dismutase (MnSOD) is one of the antioxidant enzymes found in the mitochondria where it converts superoxide to hydrogen peroxide. As one of the theories regarding the pathophysiology of TD involves increased oxidative stress, the MnSOD gene has been proposed as a candidate for TD [31]. Several studies of the Ala9Val polymorphism have had inconsistent results. Bakker et al. (2008) [32] performed a meta-analysis of four studies and found an association between the Ala homozygote population and TD, contrary to prior studies. A meta-analysis of nine studies did not find an association between this polymorphism and TD [33].

Heparan sulfate proteoglycan 2 (HSPG 2) is another gene implicated in TD development. Syu et al. (2010) found an association between HSPG 2/rs2445142 G allele and TD in 86 schizophrenic Japanese patients with treatment resistant TD [34]. This finding was confirmed by Greenbaum et al. (2012) in European patients in the CATIE trial and in Jewish Israeli patients [35]. Finally Zai et al. (2018) in a meta-analysis of four data sets confirmed these findings albeit not with a substantial level of significance [36]. The HSPG 2 gene codes for perlecan which is a component of the blood-brain barrier. HSPG 2 expression is reduced in rats treated with chronic haloperidol over 50 weeks [34]. The significance of this finding is not known although hypothesized to be related to alteration of the blood-brain barrier by neuroleptic use which may lead to increased brain iron levels possibly playing a role in the dopamine D2 receptor hypersensitivity seen in TD [37]. Further research on this gene is needed.

The conflicting and soft data regarding genetics and TD may represent multiple genes working in concert to produce TD symptoms. Additional risk factors may also need to be considered as they may interact with genetics to produce TD.

1.2. Pathogenesis of TD

The pathogenesis of TD is unknown, however there are several theories proposed. The “dopamine receptor super sensitivity” theory remains the most recognized. Chronic blockade of the D2 and possibly D3 dopamine receptors leads to the gradual up regulation of D2 receptors with postsynaptic dopamine receptor supersensitivity. FGA's tend to remain bound to the D2 receptors for a few days which are longer than SGA's possibly explaining the difference in development of TD between these agents. D2 receptors are inhibitory, located on medium spiny neurons and project onto the indirect pathway. Therefore, an increase in D2 receptors could result in hyperkinetic movements such as TD [38], although this is questionable [4]. There is some evidence to support the dopamine super sensitivity theory. Characteristics, such as the temporary reduction in TD symptoms with an increase in DRBA dosage can be explained by this theory.

Sudden withdrawal of DRBA, known to exacerbate TD symptoms, can also be explained by this theory [4]. Finally, an increased number of D2 receptors have been found to correlate with vacuous chewing movements in the rat model of TD [4]. (Rats given haloperidol for a prolonged period will develop mouth and tongue movements known as vacuous chewing movements. This has served as an animal model for TD.)

However, this theory does not explain the chronicity of TD as the DRBA blockade of the dopamine receptors is not permanent. The time course of development does not match either as the development of D2 receptor supersensitivity occurs within days to weeks and TD develops after months to years. Additionally, the ability to mount a dopamine supersensitivity response declines with increasing age and TD appears to increase with advanced age [39]. Finally, as the dopamine supersensitivity response is expected to be universal, TD does not develop in everyone taking DRBA's.

The “neurodegenerative” hypothesis of TD proposes a neurotoxic process which would explain the chronicity of TD symptoms. Neurotoxic mechanisms such as the production of lipid peroxidation and free radical formation by chronic DRBA use could lead to neuronal damage and degeneration [39]. Treatment of schizophrenia patients with DRBA's is associated with 15% per decade loss of dopamine neuron transporters as compared to the natural loss of 5% per decade. This is suggestive of a more rapid rate of dopamine neuron loss due to accumulation of the drug in the neuromelanin of the substantia nigra [40]. The neurodegenerative hypothesis eventually merged with the “oxidative stress” hypothesis of TD as the mechanism of neurotoxicity became free radical formation [38]. Chronic use of DRBA would induce increased dopamine synthesis and metabolism. Increased dopamine turnover is thought to produce an increase in free radicals [31,39]. This in combination with impairment of the antioxidant system leads to oxidative stress which has been found with chronic DRBA exposure. Additionally the level of MnSOD, the antioxidant enzyme, is elevated in those with TD compared to those without TD and the Ala9Val polymorphism in the MnSOD gene has been associated with TD [31]. Slow accrual of oxidative damage can take months to years to increase to the extent where there may be an observable clinical effect which is consistent with the time course of TD development [39]. Evidence in support of the oxidative stress theory include animal studies treated with FGA's associated with increased free radical activity and vacuous chewing movements which may be preventable with antioxidant treatment such as selegiline and vitamin E [39]. Clinical studies involving humans have found an increase in lipid peroxides in plasma and CSF in those treated with antipsychotics, however, an association between medication and changes in antioxidant enzymes are less convincing [39]. Furthermore, treatment of TD with antioxidants such as vitamin E has not been found to be clinically effective [41].

Another hypothesis regarding the pathogenesis of TD is the “maladaptive synaptic plasticity” hypothesis. Synaptic plasticity refers to the increase or decrease of synaptic neurotransmission based on prior experience and has been thought to underlie many hyperkinetic disorders such as Huntington's disease, Tourette's syndrome and levodopa induced dyskinesia [4]. Synaptic plasticity is modulated by the cholinergic, GABAergic and dopaminergic systems. DRBA's are thought to impair neocortical synaptic plasticity. According to this hypothesis, D2 receptor hypersensitivity leads to changes in the glutamatergic synapses on striatal interneurons which result in an imbalance between the direct and indirect pathways producing abnormal output to the sensorimotor cortex. Simultaneously, chronic DRBA use causes maladaptive neocortical plasticity which when combined with the basal ganglia's abnormal output produce abnormal movements and symptoms of TD [4]. This maladaptive synaptic plasticity explains the chronicity of TD symptoms. However, further research is needed to confirm this hypothesis.

2. Conclusions

TD is a potentially preventable condition; however recognizing patients who will develop the condition is difficult. Limiting DRBA's, especially avoiding FGA's in the elderly may help to prevent TD; however there appears to be a genetic influence which cannot be avoided. Plus there may be some gene-gene interactions that have not yet been discovered. The pathogenesis of TD is currently unknown; however there appear to be three main theories: dopamine receptor supersensitivity, oxidative stress and the maladaptive synaptic plasticity theory. There seems to be some evidence for each theory but none completely explains this complex condition.

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