*International Journal of Research and Review*
*DOI: https://doi.org/10.52403/ijrr.20210953*
*Vol.8; Issue: 9; September 2021*
*Website: www.ijrrjournal.com*
*Review Article* *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

# Drug-Induced Tardive Dyskinesia

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## ABSTRACT

Drug-induced movement disorders could be classified into acute, subacute, and chronic based on the time of occurrence. Tardive dyskinesia (TD) is one of the most frequent long-term drug-induced movement disorders. Delay in treatment often caused TD to be irreversible. In this review, we will discuss TD in-depth to enhance clinician knowledge regarding the diagnosis, prevention, and comprehensive management of patients with TD.

***Keywords***: tardive dyskinesia, movement, disorder, antipsychotic

## INTRODUCTION

Drug-induced movement disorders are one of the main problems faced in all parts of the world. There is still no data on the global prevalence of movement disorders. A 3-year prospective multicentre study conducted in Europe reported the prevalence of drug-induced movement disorders of 39%.[1] The prevalence of drug-induced movement disorders was 44% in Ethiopia.[2] Until date, there is no specific study of the prevalence of drug-induced movement disorders in Indonesia.

Movement disorders related to drugs can be classified into acute, subacute, and chronic based on the time of occurrence.[3,4] One of the acute movement disorders is akathisia which occurs shortly after the drug is administered. Drugs-induced chronic movement disorders can be presented as tardive dyskinesia and tardive dystonia. These disorders occurred mostly in the administration of antipsychotics.[5] Patterson et al reported the prevalence of patients with movement disorders was 28.4% on the 6-month course of typical antipsychotics.[6] The most common types of chronic movement disorders are akathisia and tardive dyskinesia.[7]

Tardive dyskinesia (TD) is a myriad of slow-onset symptoms and persistent involuntary movements caused by long-term exposure to dopamine receptor blocking agents (DRBA). The word "tardive" comes from the Latin word "tardus" which can be interpreted as the late onset of the disorder. The prevalence of TD varies greatly between countries, ranging from 5.9% to 30%.[4,8–10] A cross-sectional study conducted in Padang, Indonesia, found that the prevalence of TD in outpatient schizophrenia patients was 40%.[11]

Drug-induced movement disorders, including TD, are often challenging for clinicians because there is no definitive risk factor that can predict the occurrence of TD.[12] The existence of TD is also associated with worse social stigma regarding treatment for the mental disorder, decreased quality of life, and poor compliance.[13,14] There is also a gap in the management of TD. Replacing drugs with minimal side effects or dose reduction is still questionable for TD. This gap is widened by the fact of limited current therapeutic modalities[15] with suboptimal outcomes.[12] Despite current evidence of this disorder, progress in prevention and treatment of TD has been slow. Lacking updated information also creates a barrier in the diagnosis and management of patients.[2]

Early identification of TD can avoid future complications, however, the presenting symptoms may be atypical.[12] The earlier the condition of TD is treated, the fewer complications that will arise.[2] Therefore, it is very important for clinicians to diagnose and treat TD as quickly as possible. Delay in treatment often causes TD to be irreversible.[12,16] This paper aims to enhance clinicians' knowledge regarding TD so prompt diagnosis, preventive measures, and comprehensive management of patients with TD could be performed in real practice.

## Classification, Epidemiology, and Risk Factor

Drug-induced movement disorders occur most frequently with antipsychotics.[5] The typical (first generation) antipsychotic is known to be the most common cause of movement disorders. Second-generation antipsychotics have a higher affinity for 5-$HT_2$ receptors than dopamine D2 receptors. The binding of dopamine receptors in second-generation antipsychotics is significantly weaker, resulting in fewer side effects of movement disorders.[17] This was confirmed by the European First-Episode Schizophrenia Trial (EUFEST) study which reported a higher prevalence of drug-induced movement disorders with typical antipsychotics (34%) compared to atypical antipsychotics (28%).[18]

Drug-induced movement disorders can be divided into several groups based on the onset: acute (occurring within hours to days), sub-acute which occurs within days to weeks after the administration of antipsychotics[13] (including dystonia, parkinsonism, and akathisia)[19] and chronic disease occurring several months after antipsychotic therapy (including tardive dyskinesia and tardive dystonia).[15]

A systematic review involving 4 studies by Corell et al. found the prevalence of TD was 15.6% in patients not taking antipsychotics, 32.4% in first-generation antipsychotics, and 13.1% in second-generation antipsychotics.[20] Corell et al. also conducted a study of 12 studies and found the incidence of TD in adults receiving typical antipsychotics was 7.7% compared to 5.2% in the elderly.[20] Another study reported the incidence of TD associated with typical long-term antipsychotics was 5% per year with a cumulative annual rate of 25-30% in the elderly.[19]

Misgana et al. performed a multivariate analysis of patients with TD. The study found 51% patients were over 45 years old (Odds Ratio (OR) = 2.39, 95% CI: 1.07-6.38) and 55% of patients were women (OR = 2.51, 95% CI: 1.08-5.86).[2] These findings indicate that women and age > 45 years are at risk of developing TD. Other TD risk factors can be seen in Table 1.

**Table 1. Risk Factors for TD[13,15,21]**

| **Unmodifiable risk factors** | **Modifiable risk factors** |
|---|---|
| - Women (usually have more severe TD symptoms)<br>- Old age (Individuals more than 45 years old had 2.5 times higher risk to develop TD compared to 15-29 years)<br>- Taking high doses of antipsychotics<br>- Taking chlorpromazine > 400 mg<br>- Diagnosis of affective and substance disorders, including alcohol<br>- History of drug-related parkinsonism in the early phase<br>- Using anticholinergic and anti-parkinsonian drugs<br>- Intermittent neuroleptic management | - Using the first generation of anti-psychotics<br>- Alcohol consumption<br>- Long-term use of antipsychotics (Using antipsychotic more than 5 years is 2.43 times more likely to develop TD than using antipsychotic < 1 year) |
| - Comorbidities (diabetes mellitus)<br>- Race (Asian had a lower risk of developing TD compared to African and American) | |

## Pathophysiology

The pathophysiology underlying the occurrence of TD is thought to be through several pathways. One of them is that long-term post-synaptic dopamine receptor blockade causes supersensitivity of dopamine in the basal ganglia area, which involves the upregulation of dopamine 2 (D2) receptors.[21–23] Several studies have also found that D3 and D5 receptors are

involved in the pathogenesis of TD.[24] D2 receptors are inhibitory receptors expressed on the medium spiny neurons in striatal which acts by blocking inhibitory pathways and resulting indirectly in hyperkinetic movements.[25]

The imbalance of neurotransmitters is one of the hypotheses underlying the occurrence of TD. The administration of anticholinergics along with dopamine receptor hypersensitivity will cause an imbalance of both neurotransmitters, hence, resulting in TD. Serotonin imbalance is thought to play a role in TD. The use of other drugs, such as selective serotonin reuptake inhibitors (SSRIs) will inhibit dopamine in the nigrostriatal pathway by increasing serotonin in the rape nuclei.[22,26] In addition, the inhibitory effect of serotonin on dopamine production in the basal ganglia by SSRI, will disrupt dopamine production, which causes TD.[22]

Previous reports have also suggested the involvement of Gamma-aminobutyric acid (GABA) in TD. Drug-induced GABA nerve damage will interfere with GABA function in the striatum, the region of the brain involved in the movement of oral muscles. Available evidence also suggests that GABA neurons will directly inhibit dopamine in certain brain regions.[27] Other underlying hypotheses causing TD were associated with increased effects of endogenous opioids, glutamate excitotoxicity, oxidative stress, and genetic susceptibility.[21–23]

Fedorenko et al. stated that the presence of the PIP5K2A gene was associated with schizophrenia, but it could be mutated in TD. The PIP5K2A gene is protective against neurotoxicity that causes TD.[28] TD is also associated with dopamine D3 Ser9Gly receptor gene polymorphisms and serotonin 2A and 2C gene receptors.[29] This gene polymorphism supports drug administration-associated dopamine receptor hypersensitivity.[22]

TD may also occur due to dose reduction or abrupt discontinuation of antipsychotics.[30] Other drugs such as antidepressants (e.g., duloxetine),[26] mood stabilizers (lithium),[31] and calcium channel blockers (e.g., flunarizine) have been reported to trigger TD (e.g., flunarizine). Table 2).[22]

**Table 2. Drugs related to TD[22]**

| Drugs | Mechanisms | Additional Information |
|---|---|---|
| Antipsychotic | Bind to dopamine D2 Receptors<br>Certain butyrophenones can induce TD through pro-inflammatory cytokine influx | Frequently seen in typical antipsychotics use. Some atypical antipsychotics may increase the risk of developing TD (aripiprazole, risperidone, and amisulpride).[32–34]<br><br>Mostly found in typical antipsychotic treatment (30%) and 20,7% in atypical antipsychotic treatment. |
| Anticholinergics | | Procyclidine in COPD is associated with reduced symptoms of Parkinson's disease. These agents are known to worsen TD and impair cognitive function. Anticholinergic effects on TD may be reversible.[35] |
| Antidepressants | Increases monoamine levels (dopamine, serotonin, and norepinephrine) | TD associated with antidepressants are less common. Trazodone, doxepin, clomipramine, and amitriptyline may induce TD without a history of exposure to antipsychotics. Amisulpride is known to have less frequent extrapyramidal side effects. |
| Antiemetics | The dopamine antagonist | Metoclopramide is associated with respiratory dyskinesia. It may cause gasping, abnormal breathing, and irregular movement of the esophagus.[36]<br>The use of prochlorperazine increases the risk of TD compared to metoclopramide.[37] |
| Anticonvulsant | Inhibits sodium channels, increases GABA function | Although rare, carbamazepine and lamotrigine have been reported to be associated with TD.[38] |
| Antihistamines | Antagonist of histamine receptor | Hydroxyzine is associated with the incidence of TD in long-term use (reported in 7.5 months of usage). |
| Decongestant | Alpha-adrenergic agonists | Alpha antagonists are known to reduce symptoms of dyskinesia, hence alpha agonists were possible to worsen TD. |
| Antiparkinsonian | Increases dopamine or decreases acetylcholine activity | The use of L-Dopa can trigger dyskinesia, especially in early-onset Parkinson's. Anticholinergic antiparkinsonian agents will block muscarinic receptors and decrease cholinergic activity. These agents will correct the imbalance of dopamine and acetylcholine in the striatum. |

| *Table 2 Continued...* | | |
|---|---|---|
| Anxiolytics | GABA agonists | Drugs used for anxiety including barbiturates, benzodiazepines, carbamates, and opioids. The use of clonazepam is associated with TD when discontinued abruptly. Withdrawal emergent dyskinesia occurs due to hypersensitivity to dopamine receptors. |
| Biogenic amines | Monoamine raw materials | High levels of tyramine in the blood can cause stress associated with TD. |
| Mood stabilizers | Lithium: reduces excitatory neurotransmission and increases inhibitory neurotransmitters | Consists of lithium and anticonvulsants. The use of lithium with antipsychotics increases the risk of developing BP when compared with only lithium. |
| Stimulant | Caffeine adenosine receptor antagonists<br>Amphetamine: inhibits monoamine metabolism, prevents monoamine reuptake, increases monoamine release from vesicles, and transfers monoamine to the presynaptic for subsequent release. | Including caffeine, nicotine, guarana, ginseng, amphetamine, ephedrine, and methamphetamine. High doses of caffeine (>1,000 mg) can exacerbate TD symptoms. Amphetamines and methamphetamine are associated with dyskinesia and other movement disorders.[39] |

## Diagnosis of Drug-Induced Tardive Dyskinesia

Symptoms of TD are characterized by repetitive and involuntary movements that usually occur in the face, mouth, tongue, and extremities.[40] Symptoms vary from mild to severe, with localized or diffuse involuntary movements. TD can also be provoked by stress.[21]

Antipsychotic side effects also often cause drug-induced Parkinsonism (DIP) immediately after drug administration. The underlying pathophysiology of DIP and TD is different. It is important for clinicians to clearly define these side effects since their management options are also different. Symptoms of DIP and TD are generally different (Table 3), but they can occur simultaneously.[41]

Diagnosis of TD uses the Schooler-Kane criteria and identification of antipsychotic drugs that can cause TD. Abnormal Involuntary Movement Scale (AIMS) was a rating scale used to measure the severity of tardive dyskinesia.[42] Diagnosis of TD using Schooler-Kane must meet three criteria:[41]

a. Symptoms occur for at least 3 months of antipsychotic therapy.
b. Abnormal involuntary movements must occur in 2 or more body regions (mild) or 1 body region if symptoms are moderate to severe as determined by the AIMS scale.
c. There are no other conditions that might cause abnormal movements.

**Table 3. Differences between *Drug-Induced Parkinsonism* and *Tardive Dyskinesia*[41]**

| **Symptoms** | ***Drug-induced Parkinsonism*** | ***Tardive dyskinesia*** |
|---|---|---|
| Onset | Immediately (within a few hours to weeks) after an antipsychotic is given or after a dose is increased | Late (months to years) after antipsychotic therapy |
| Visible motor symptoms | Rhythmic tremor, rigidity, shuffling gait; akathisia may occur simultaneously | Unrhythmic (usually choreo-athetoid) movements of the face, trunk, and extremities |
| Effects (hours to weeks) after increasing the antipsychotic dose | Symptoms worsen | Symptoms improve |
| Short effects (hours-days-weeks) after a decrease in antipsychotic dose | Symptoms improve | Symptoms worsen |
| Effects of anticholinergic administration | Symptoms improve | Symptoms can be severe |
| Pharmacotherapy treatment options | Anticholinergics (e.g., benztropine), amantadine | Inhibitor VMAT2 (tetrabenazine, valbenazine, deutetrabenazine), ginkgo biloba, clonazepam, amantadine |

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) classifies TD as a drug-induced movement disorder that occurred after drugs discontinuation, dose change, or reduction. In all cases, symptoms of TD must persist for at least 1 month after treatment is discontinued.[43] Baseline evaluation using AIMS must be performed as soon as possible after TD was diagnosed and treated initially.[42]

**Management**

TD is difficult to treat clinically because the exact mechanism is not entirely clear. TD is generally misdiagnosed as a mental disorder rather than a neurological disorder which may be prescribed more antipsychotics and resulted in worsening of the current condition. The definitive classification of TD is necessary to prevent such problems to reoccur.[22]

The American Psychiatry Association (APA) recommends monitoring the occurrence of TD for 3-12 months in schizophrenia patients, depending on risk factors and the type of antipsychotic used. Evaluations are performed every 6 months for patients taking typical antipsychotics and 12 months for patients taking atypical antipsychotics.[41]

One of the recommended TD managements is to stop the causative drug if possible.[21] Approximately 60% of TD cases will experience improvement after drugs are discontinued.[41] Clinicians need to be cautious of withdrawal symptoms which may occur after discontinuing the drug abruptly and leading to TD or withdrawal-emergent dyskinesia.

Several previous studies reported the advantage of clozapine in the management of TD.[15,44] Switching typical to atypical antipsychotics has no clear evidence in patients requiring antipsychotics[45] since it does not reduce TD symptoms and has a higher risk of relapse for the psychotic symptoms. Clinicians should use the lowest possible dose as the psychotic symptoms are controlled, followed by evaluating TD symptoms whether they interfere with daily activities or quality of life. As the presenting symptoms are classified as mild, it is recommended to observe and evaluate the current symptoms.[45] Intervention using suppressive agents is recommended when the symptoms hinder daily activity.[41] Further management algorithm for TD can be seen in Figure 1.

The American Academy of Neurology (AAN) recommends levels of evidence A to C for treating TD. Level A is defined as treatment with proven efficacy, level B is defined as treatment with probable efficacy, while level C is defined as potential efficacy.[41]

**VMAT-2 Inhibitor (Level A)**

The recommended pharmacotherapy agents (Level A) are vesicular monoamine transporter type 2 (VMAT-2) inhibitors, velbenazine, and deutetrabenazine (Deut-TBZ). The mode of action of this agent is related to dopamine D2 receptor hypersensitivity due to chronic D2 receptor block.[41,45] Inhibition of VMAT-2 will increase cytoplasmic dopamine levels, decrease dopamine release at the synapse, and stimulate postsynaptic receptors, ultimately reducing TD symptoms.[41]

The recommended dose of valbenazine is 40 mg per day. It should be noted that side effects, such as somnolence, fatigue, and sedation may arise. Valbenazine should not be used in patients with arrhythmias because it can prolong the QT interval. The recommended dose of deutetrabenazine is 6 mg/day with possible side effects, such as depression, suicidal ideation, neuroleptic malignant syndrome, agitation, parkinsonism, and QT prolongation. Deut-TBZ is contraindicated in untreated depression, liver disease, or using monoamine oxidase inhibitors. Patients who do not have access to both drugs are advised to use clonazepam or ginkgo Biloba.[45]

**Clonazepam (Level B)**

The benzodiazepines have been reported to induce TD, but some evidence suggests that benzodiazepines may be used to treat TD. Sharma et al reported the use of clonazepam in a patient with TD due to long-term use of trifluoperazine, citalopram, trihexyphenidyl, and propranolol.[46] The dose of clonazepam is started at 0.5 mg and titrated slowly. Dosage is not recommended to exceed 4.5 mg per day.[45]

**_Ginkgo Biloba_ extract (Level B)**

The recommended dose of *Ginkgo Biloba* extract (EGb-761) is 240 mg per day.[45] *Ginkgo biloba* is usually used to improve cognitive function in patients. A randomized, double-controlled trial in 157 schizophrenic patients comparing EGb-761 with placebo found lower AIMS scores of TD (2.13 ± 1.75 vs 0.10 ± 1.69; P < .0001).[47]

**Cholinergic Agent**

The use of Donepezil (acetylcholinesterase inhibitor) could reduce TD symptoms.[48] A meta-analysis conducted by Tammenmaa-Aho et al in 2018 reported the available evidence to date is scarce and existing studies have weak evidence.[49]

**Other antipsychotics**

Clozapine acts as a dopamine and serotonin receptor antagonist. Clozapine is currently the recommended drug for patients who require antipsychotics and have symptomatic TD.[50] However, the AAN Guidelines reported clozapine has a U level where it does not produce significant results.[45] Other drugs with similar function as clozapine, such as quetiapine (a weak antagonist of the striatal dopamine pathway) and olanzapine (a dopamine and serotonin receptor antagonist) are known to be effective in improving TD symptoms.[51]

**Beta-blockers**

Propranolol is a beta-adrenergic receptor antagonist used to treat hypertension and arrhythmias. Hatcher-Martin et al. used low-dose propranolol in 47 TD patients who persisted for 17 months and found low-dose propranolol to improve symptoms in 64% of patients.[52]

**Amantadine (Level C)**

Amantadine is a non-competitive glutamate receptor antagonist which increases presynaptic dopamine release and inhibits presynaptic dopamine reuptake. Amantadine is effective in the management of L-Dopa-induced TD in patients with parkinsonism.[22,45]

**Branched Chain Amino Acids (BCAAs)**

The use of branched-chain amino acids has also been reported to reduce TD symptoms by decreasing plasma levels of phenylalanine-BCAAs act by reducing the accumulation of tyrosine and other amino acids that act as dopamine precursors, thereby reducing dopamine synthesis in the central nervous system. BCAAs are also known to be effective in reducing TD symptoms with antipsychotic use.[22]

**Prevention**

Precautionary measures are recommended. Administration of antipsychotics or other drugs that can trigger TD should be accompanied by education by giving the lowest dose of medication.[22] Clinicians should consider giving antipsychotics as indicated in the shortest period and the lowest possible dose according to the patient's condition. Patients with a history of anticholinergic use should be discontinued slowly if TD symptoms develop.[22]

One of the proposed mechanisms of TD is the production of neurotoxic free radicals due to the metabolism of antipsychotic drugs. Hence, consuming high antioxidants foods may help in TD. This is claimed to prevent the onset of TD.[22]

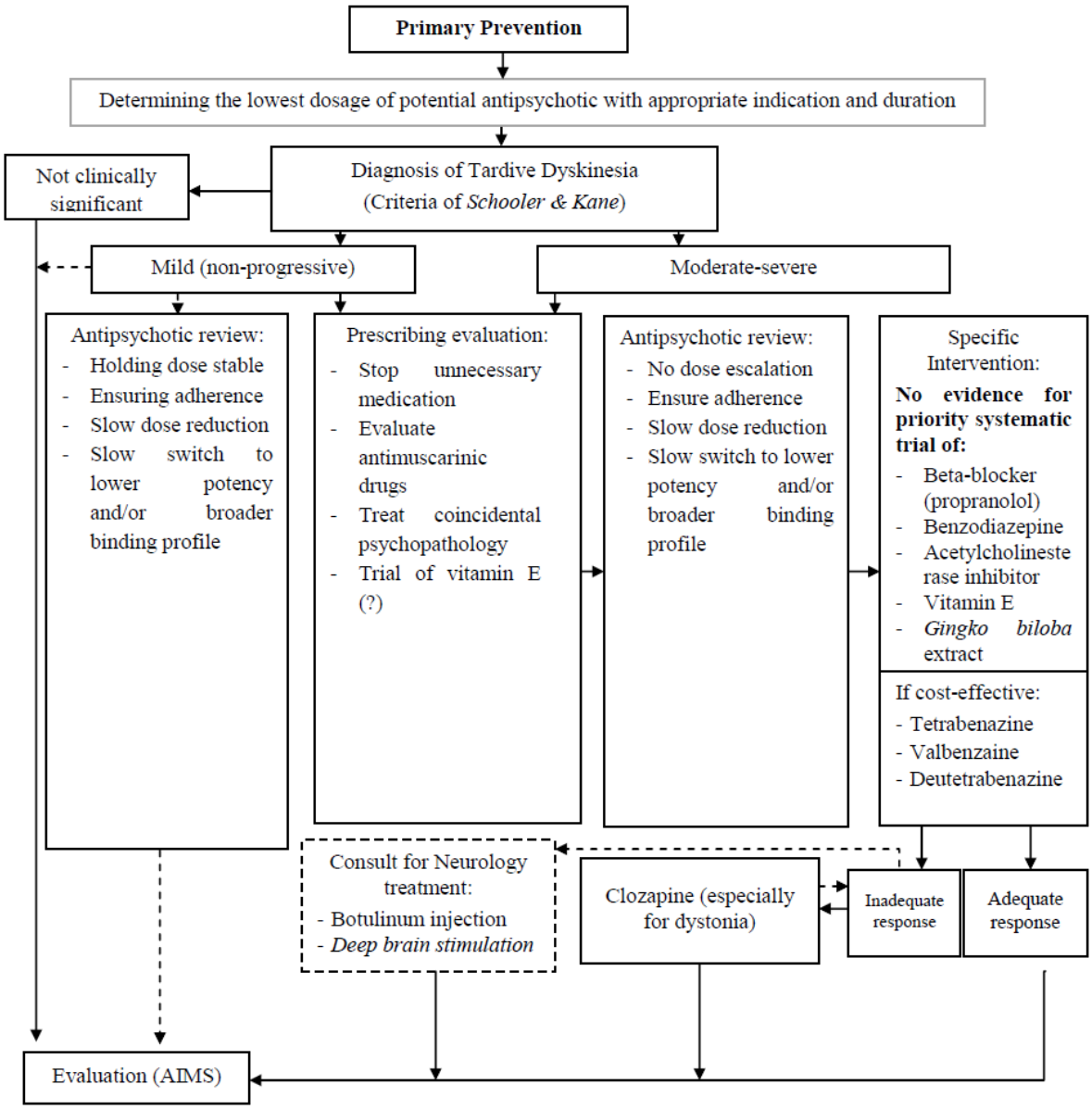


**Figure 1. Management Scheme of *Tardive Dyskinesia*[45,53]**

## CONCLUSION

Long-term use of medications in patients with mental disorders often causes tardive dyskinesia. A variety of drugs can cause TD, but most common medication causes TD is antipsychotics. The proposed pathophysiology of TD is dopamine receptor supersensitivity, imbalance of monoamine, glutamate, and GABA neurotransmitters, along with the role of oxidative stress and genetic susceptibility. TD can be diagnosed by using the Schooler-Kane and DSM-V criteria. AIMS is a rating scale to measure and evaluate the severity of TD. The main management is preventing TD occurrence and prescribing antipsychotics at the lowest possible dose. In contrast to other drug-induced movement disorders, TD is often challenging to treat for clinicians. Clinicians should always carry out regular education and assessments regarding the risk of developing TD. Apart from being irreversible, TD can affect social stigma and quality of life significantly.

**Acknowledgement:** None

**Conflict of Interest:** None

**Source of Funding:** None

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How to cite this article: Marianto M, Kosim H, I Made Wedastra. Drug-induced tardive dyskinesia. *International Journal of Research and Review*. 2021; 8(9): 413-422. DOI: *https://doi.org/10.52403/ijrr.20210953*

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