THERAPEUTIC ADVANCES in
Psychopharmacology

Review

Current perspectives on the epidemiology and burden of tardive dyskinesia: a focused review of the clinical situation in Japan

Ther Adv Psychopharmacol

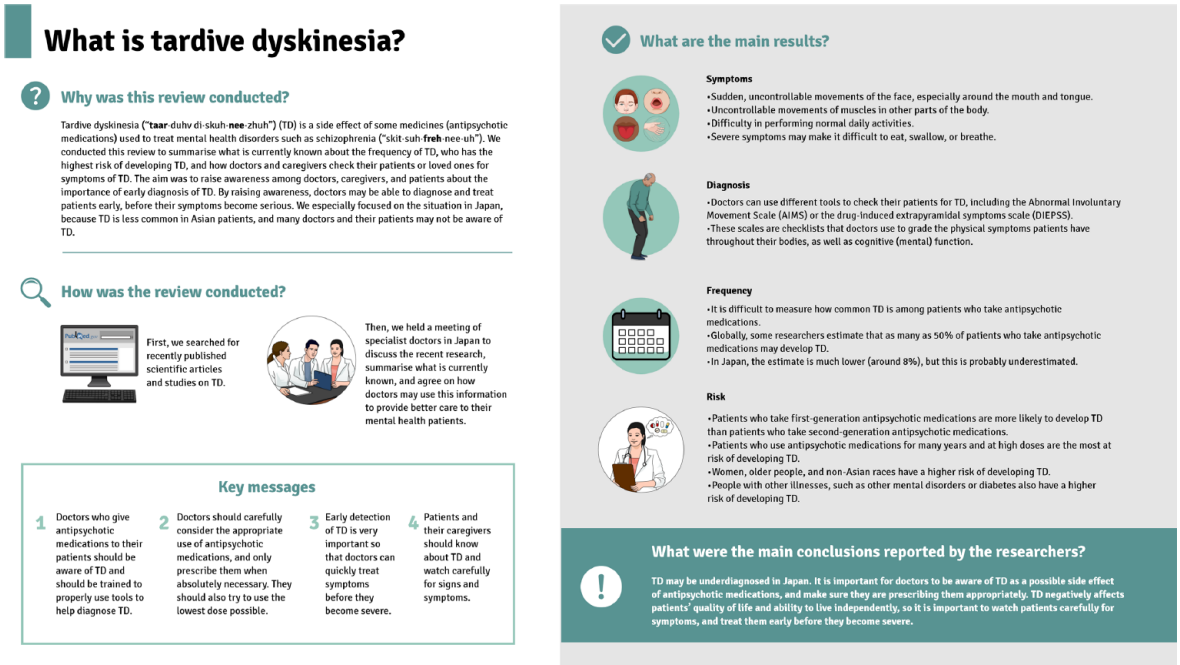
2022, Vol. 12: 1–15

DOI: 10.1177/20451253221139608

Yasuhiro Mori, Hiroyoshi Takeuchi and Yuichiro Tsutsumi

***Abstract*:** Tardive dyskinesia (TD) is a movement disorder that can develop with the use of dopamine receptor-blocking agents and is most commonly caused by antipsychotics. The use of antipsychotics is expanding, which may lead to an increased number of patients experiencing TD. To summarise the current knowledge of the epidemiology and risk factors for TD in Japan, we reviewed articles related to the current state of knowledge around TD identified through a PubMed search, and held a roundtable discussion of experts in Japan on 9 September 2021 to form the basis of the opinion presented within this review. The true prevalence of TD among patients treated with antipsychotics is not well characterised; it is reported to be between 15% and 50% globally and between 6.5% and 7.7% in Japan. Potential barriers to timely treatment of TD include the stigma surrounding mental health issues and the lack of data regarding TD in Asian patients. This review summarises the current knowledge of the epidemiology, challenges to TD diagnosis and risk factors for TD in Japan. Recent strategies for symptom monitoring and early diagnosis, as well as consensus recommendations are included. Achieving a high level of awareness of TD among physicians who treat patients with psychiatric disorders is of great importance and physicians should ensure that patients with psychiatric disorders receiving antipsychotics are proactively monitored for signs of TD.

Plain Language Summary



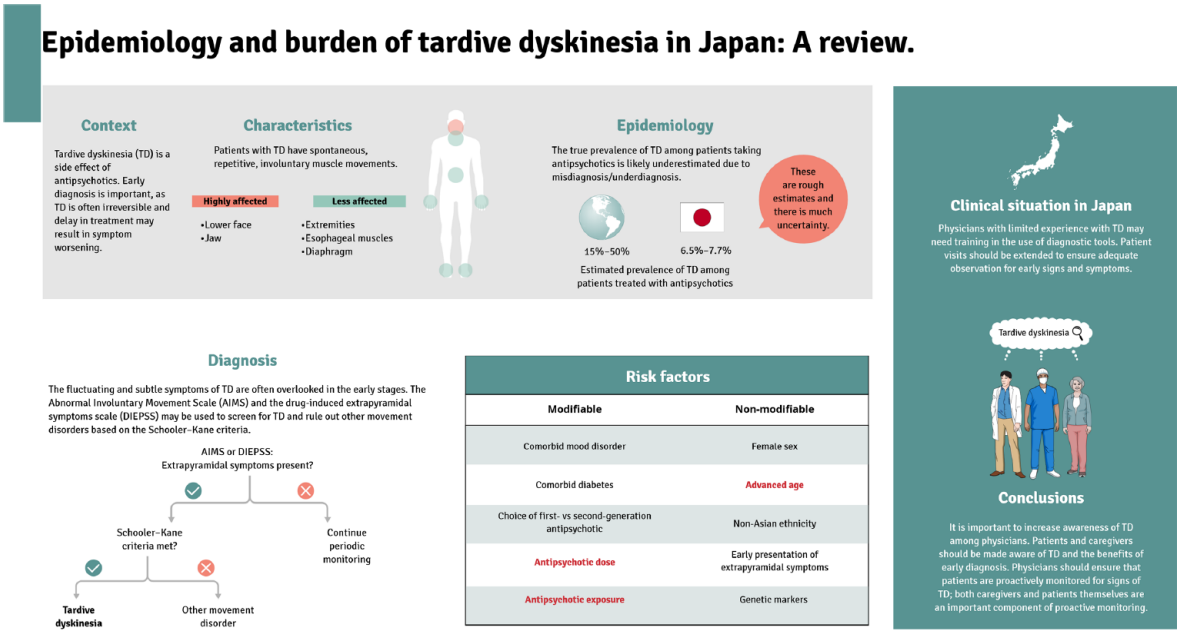
Plain Language Summary (In Japanese)

Correspondence to:
Yasuhiro Mori
Department of Psychiatry, Aichi Medical University, 1-1 Yazako-karimata, Nagakute 480-1195, Aichi, Japan.
ymkmori@aichi-med-u.ac.jp

Hiroyoshi Takeuchi
Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan

Yuichiro Tsutsumi
Ongata Psychiatric Hospital, Tokyo, Japan

Visual Summary



Visual Summary (In Japanese)

Keywords: antipsychotics, burden, Japan, risk factors, schizophrenia, tardive dyskinesia

Received: 23 March 2022; revised manuscript accepted: 28 October 2022.

Introduction

Tardive dyskinesia (TD) is a movement disorder that occurs as a potentially serious adverse drug reaction to various psychotropic medications, the most common of which are antipsychotics.[1,2] TD is classified in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth edition (*DSM*-5) as 'involuntary athetoid or choreiform movements lasting at least a few weeks, developing in association with the use of a neuroleptic medication for at least a few months, and persisting beyond 4–8 weeks'.[3] TD is more commonly observed in patients treated with first-generation antipsychotics (FGAs) than with second-generation antipsychotics (SGAs),[4–8] yet the increasing use of SGAs for treatment of affective disorders in addition to schizophrenia suggests that the prevalence of TD will likely continue to increase.[9]

The symptoms of TD include spontaneous, repetitive and involuntary muscle movements, frequently of the lower face and jaw, and sometimes unwanted movements of the extremities, hindering walking or the use of hands.[10,11] The burdens of patients with TD include not only impairments in activities of daily life and the social stigma associated with uncontrollable facial expressions or disfigurement, but in rare cases where the pharyngeal, diaphragm or trunk muscles are involved, TD can also be life-threatening.[12–14] TD is often irreversible, even when antipsychotics are discontinued.[15,16]

Although progress has been made in Japan in recent decades to address the stigma associated with mental illness,[17] public perception of mental illness in Japan remains problematic, as the belief persists that illnesses such as schizophrenia and major depressive disorder commonly result from a patient's own character flaws or the way he or she was raised.[18] This stigma may present a considerable barrier to treatment for patients struggling with mental health issues; there is a need to better understand the situation in Japan with

respect to treatment and patient or caregiver burden, particularly regarding side effects of antipsychotics. Moreover, there is a lack of data specifically in Asian patients, who are less likely to suffer from TD than other races.[19]

The purpose of this review is to summarise the current knowledge of the epidemiology and risk factors for TD with a special focus on Japan, and to describe the recent strategies for symptom monitoring and early diagnosis, as discussed at the recent roundtable discussion of experts in Japan. A detailed review of the pathophysiology and current treatment options for TD, as well as the prognosis for TD, is included in the second article of the supplement.

Methods

To identify suitable literature to include in this review, we conducted a PubMed search in August 2021 focusing on articles published between January 2000 and August 2021, although articles published prior to 2000 were included as appropriate. The following search terms were used: 'tardive dyskinesia', alone and in combination with 'epidemiology', 'incidence', 'prevalence', 'atypical antipsychotics', 'risk factors', 'mortality rate', 'quality of life', 'Asia', and 'Japan'. Details of the literature search are described in the flow diagram shown in Supplementary Figure 1. A roundtable discussion, which was held on 9 September 2021, formed the basis for the expert opinion presented in this article. We prioritised the inclusion of systematic reviews and meta-analyses in addition to original articles as materials for the roundtable discussion, and discussed narrative reviews where appropriate. Case reports and case series were excluded. We prioritised English publications but also included Japanese articles where relevant, particularly with respect to the clinical situation in Japan. Among those who attended the roundtable discussion, the authors of this review as well as Professor Koichiro Watanabe (Department of Neuropsychiatry, Faculty of Medicine, Kyorin University, Japan) contributed to the consensus recommendations.

The roundtable discussion was moderated by a representative of the sponsor, Mitsubishi Tanabe Pharma Corporation. Discussions were facilitated by Professor Watanabe, who also recommended the panellists to be invited to participate, based on their clinical and academic experience as well as their participation in scientific congresses in Japan. In addition to Professor Watanabe, the panellists included the authors of this article. The discussion was structured as follows: the first half began with a 15-min review of the recent literature concerning TD epidemiology, risk factors and symptoms or diagnosis, followed by a 30-min discussion among the panellists concerning the following questions: (1) Epidemiology: Is TD onset similar in Japan compared with other countries? Are there any concerns specific to Japan, such as the clinical environment or the drugs used to treat the underlying psychiatric disease? (2) Diagnosis: Are there any particularly important signs or symptoms to monitor for? What should physicians be cautious of with respect to differential diagnoses? Are there any challenges to be aware of for the use of evaluation scales such as the Abnormal Involuntary Movement Scale (AIMS) and drug-induced extrapyramidal symptoms scale (DIEPSS)? (3) Risk factors: What are the risk factors that physicians should be aware of, and how can they be mitigated? The second half of the discussion included topics covered in the second article of this supplement. The entire discussion was recorded and minutes were taken in Japanese and translated into English. The authors collaborated with the medical writer to structure the content into this review article. All participants consented to publication of the article, and non-author contributors have been mentioned in the acknowledgement.

Epidemiology of TD

The prevalence and incidence of TD in the general population are difficult to estimate, as the existing literature generally describes the epidemiology of TD with respect to patients with psychiatric disorders (i.e. those receiving antipsychotics).[9] Estimates for the global prevalence of TD among those treated with antipsychotics vary considerably, from 15% to as high as 50%,[1,2] and the prevalence is understood to be higher among patients treated with FGAs than SGAs. A large meta-analysis of 41 studies found an overall TD prevalence of 25.3% [95% confidence interval (CI), 22.7–28.1%] among patients treated with antipsychotics, whereas the prevalence for patients treated with FGAs and SGAs was 30.0% (95% CI: 26.4–33.8%) and 20.7% (95% CI: 16.6–25.4%), respectively.[20] Another meta-analysis conducted by the same group, which analysed the annual incidence of TD among patients receiving antipsychotics, found a similarly elevated risk of developing TD for patients treated with FGAs [6.5%

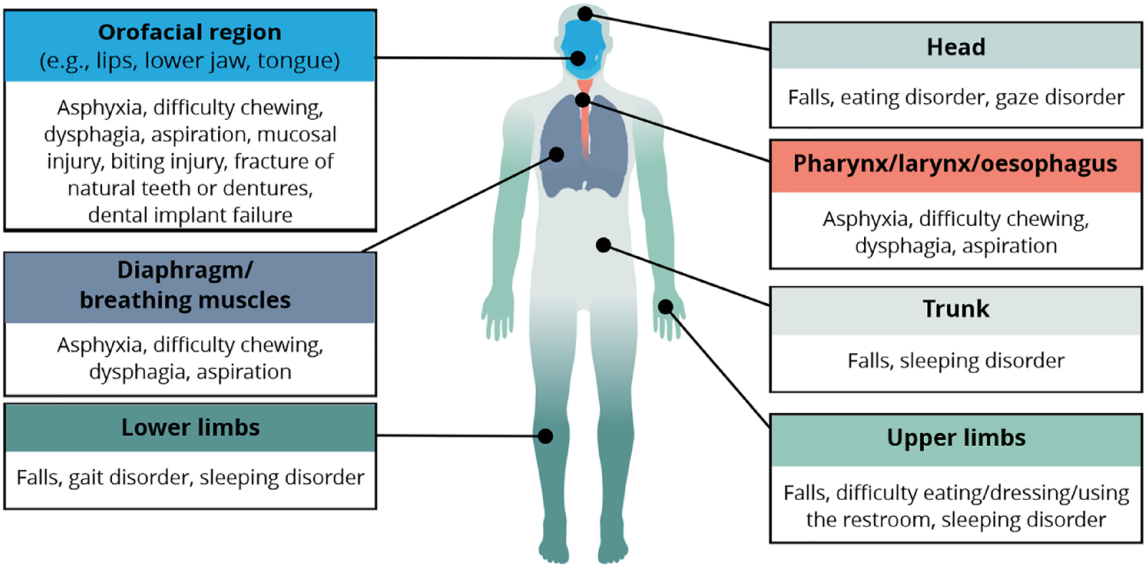


Figure 1. Negative impacts of tardive dyskinesia on activities of daily living.[a]
[a]Although not commonly experienced as a primary symptom, pain may also be reported by patients secondary to symptoms such as teeth clenching or as a result of oral injury due to involuntary movements.

(95% CI: 5.3–7.8%)] compared with SGAs [2.6% (95% CI: 2.0–3.1%)].[8]

With respect to differences in risk of TD associated with different SGAs, research has shown mixed results. A meta-analysis comparing various SGAs reported that aripiprazole was associated with the lowest risk of TD, with a rate ratio (RR) and 95% CI of 0.045 (0.01–0.19) *versus* FGAs. Olanzapine, risperidone and clozapine also conferred less risk of TD: 0.25 (0.19–0.34), 0.38 (0.25–0.58) and 0.39 (0.22–0.70), respectively, whereas ziprasidone, paliperidone and quetiapine were not found to be significantly different from FGAs.[8] Although this meta-analysis did not show reduced risk of clozapine *versus* other SGAs, another meta-analysis suggested that switching to clozapine may improve symptoms of TD.[21] A long-term study conducted in Europe also found that olanzapine and clozapine were associated with lower risk of TD compared with FGAs and other SGAs,[22] whereas a postmarketing surveillance study conducted in Japan did not find a significant difference between clozapine and other SGAs.[23] The limitations and often small number of treatment arms in the above studies should be considered when interpreting the results and how they should be applied to decisions for patient care.

Data describing the prevalence and incidence of TD in Japan among patients treated with antipsychotics are somewhat limited. An older epidemiological study found a mean prevalence of TD of 7.7% when including data from 13 studies conducted in Japan between 1972 and 1992, representing 7560 patients.[24] Data from the more recent Research on Asian Psychotropic Prescription Pattern (REAP) survey, which analysed the frequency of TD in inpatients with schizophrenia, found a TD prevalence of 6.5% among Japanese patients.[25] However, it should be noted that this study included only inpatients and thus may not be representative of the entire patient population, as patients with a less-severe form of schizophrenia (i.e. not requiring hospitalisation) were not included. To date, there have been no studies reporting the estimated annual incidence of TD or the incidence of TD according to treatment with FGAs *versus* SGAs among Japanese patients.

The drastic variation of prevalence and incidence estimates across studies may be at least partly explained by differences in study designs and methodological details in how data were gathered.[26] In addition, there is likely heterogeneity of subjects across studies and a failure to control for spontaneous dyskinesias.[10] Further complicating assessments of prevalence and incidence with respect to FGAs *versus* SGAs is the fact that many studies do not control for prior medication use, and the influence of prior pharmacotherapy on

development of TD cannot be ruled out. The true prevalence of TD is likely underestimated, owing to its often insidious presentation and frequent misdiagnosis as extrapyramidal symptoms of the underlying disease, rather than an adverse drug reaction.[27]

With the advent of SGAs, TD was expected to become less common as physicians tended to favour the newer drugs when treating patients with schizophrenia. However, as the indications of many SGAs continue to expand for other psychiatric disorders, the risk of TD will remain a persistent concern of increasing importance.[9] Nevertheless, schizophrenia remains one of the most common disorders for which these drugs are prescribed. The global age-standardised point prevalence of schizophrenia was estimated to be 0.28% in 2016; the prevalence did not vary widely among countries and was reported to be between 0.27% and 0.33% in Japan.[28] Interestingly, movement disorders including dyskinesia have been reported in antipsychotic-naïve patients with schizophrenia.[29–31] A systematic review reported that such patients presented with dyskinesia more frequently compared with healthy controls [odds ratio (OR): 3.59 (95% CI: 1.53–8.41)] and that movement disorders (dyskinesia and parkinsonism) were significantly more prevalent in first-degree healthy relatives of patients with schizophrenia than controls [OR: 1.38 (95% CI: 1.06–1.81)].[32]

Diagnosis of TD

TD can be challenging to diagnose because of the fluctuating nature of the symptoms, which often have a subtle presentation that can be easily overlooked or mistaken for symptoms of the mental illness itself.[26,33,34] The 'tardive' (i.e. delayed in onset) nature of TD can further complicate diagnosis as physicians may not immediately associate new symptoms with medication that has been well-tolerated for several months.[35] TD usually involves the oral, buccal and lingual areas of the face; the limbs and trunk may also be involved but tend to be less affected than the mouth and face. The associated involuntary movements are usually described as choreiform or athetoid in nature.[10,11] According to the *DSM*-5 criteria for TD, diagnosis is based on a patient exhibiting involuntary athetoid or choreiform movements typically of the tongue, jaw and extremities, that last at least several weeks and are associated with the use of antipsychotics of at least a few months' duration.[3,36]

In 1982, the Schooler–Kane criteria were proposed.[37] The Schooler–Kane criteria for a diagnosis of TD include a history of at least 3 months' total cumulative exposure to antipsychotics (continuous or discontinuous), the presence of moderate or worse dyskinetic movements in one or more body areas or mild or worse dyskinetic movements in two or more body areas (face, lips, jaw, tongue, upper extremities, lower extremities and trunk) and the absence of other conditions that may produce the observed abnormal involuntary movements.[37–39]

There are several rating scales available to aid in the assessment of TD. The AIMS was developed as a research tool by the National Institute of Mental Health and originally consisted of 12 items: 7 to measure the severity of abnormal movements in the orofacial region, upper extremities, lower extremities and trunk rated from 0 (none) to 4 (severe); and 5 that involve clinicians' global assessment of severity, patient awareness, incapacitation due to abnormal movements and mental status. The revised scale includes two additional items (edentulousness and the disappearance of abnormal movements during sleep).[39,40] The AIMS rating scale is frequently used to assess severity and location of abnormal involuntary movements, and acts as a screening tool for subsequent confirmation of diagnosis based on the Schooler–Kane criteria.[36,38,39] In addition to its use as a screening tool, the AIMS rating scale can be used to monitor changes in TD severity over time.[39] In the West, the AIMS rating scale is often used as a safety assessment to monitor for the development of TD in patients receiving antipsychotics in clinical trials.[41]

Another related rating scale is the DIEPSS, which consists of eight individual symptoms (gait, bradykinesia, sialorrhea, muscle rigidity, tremor, akathisia, dystonia and dyskinesia) and one global assessment (overall severity of extrapyramidal symptoms), rated on a scale of 0 (normal) to 4 (severe).[42,43] The DIEPSS rating scale evaluates a wider range of extrapyramidal symptoms, in addition to dyskinesia, compared with the AIMS. In Japan, the DIEPSS rating scale is generally the preferred tool for evaluating TD. Clinical trials conducted in Japan for antipsychotics use the DIEPSS as the standard rating scale to evaluate extrapyramidal symptoms, and the DIEPSS is the only such tool covered under the national health insurance system in Japan.

The key difference between the AIMS and DIEPSS rating scales is their scope; the AIMS scale only evaluates symptoms of TD, while the DIEPSS scale also evaluates other movement disorders, including symptoms of parkinsonism, dystonia and akathisia.[41] Data were compared from a large international study that used the AIMS to monitor for dyskinesia along with other rating scales to monitor for additional extrapyramidal symptoms, and a large study conducted in Japan that used the DIEPSS for monitoring, both of which compared the efficacy and safety of olanzapine or haloperidol.[41] The analysis found that treatment-emergent incidences of dyskinesia were similar between the two studies, suggesting that the two diagnostic tests were comparable in their ability to screen for TD.

Correctly diagnosing TD is imperative in terms of providing appropriate and timely treatment; however, there are many syndromes and conditions that cause abnormal movements similar to those of TD. As such, differential diagnosis should be performed. Differential diagnosis of TD is based on a history of treatment with antipsychotics and/or other dopamine receptor-blocking agents (DRBAs), recent discontinuation or dose reduction, and movement phenomenology.[44] Several conditions should be considered in the differential diagnosis, including spontaneous dyskinesias, parkinsonism, akathisia, dystonia and rabbit syndrome.[36,44–48] Extrapyramidal symptoms that are not considered TD as well as spontaneous dyskinesias should be ruled out.[47] Spontaneous and edentulous dyskinesias, which are not associated with antipsychotic exposure, are fairly common in elderly patients and those with schizophrenia who have not been exposed to DRBAs; such symptoms may be difficult to distinguish from TD.[36,46] Symptoms of DRBA-induced parkinsonism include bradykinesia, rigidity and rhythmic tremor; 50–75% of cases occur within 1 month of initiating DRBA treatment and 90% occur within the first 3 months.[49] Comparatively, TD onset is delayed and symptoms typically do not appear until $\geqslant$3 months after initiating treatment.[45] Symptoms of DRBA-induced parkinsonism are generally reversible after discontinuation of treatment.[44,45] Akathisia usually occurs in an acute or subacute form (90% of cases occur within 90 days of initiating DRBAs), although some patients may have tardive akathisia.[44] Patients with akathisia experience subjective feelings of restlessness and an urge to move, with an inability to sit or stand still.[36,44] Dystonia can occur in either acute or tardive forms, and may manifest in a paroxysmal (e.g. oculogyric crisis) or continuous fashion. Dystonic movements are usually sustained, which results in abnormal postures.[44] These symptoms may be present in some patients with TD, but to a much lesser degree than patients with diagnosed dystonia. Nevertheless, distinguishing dystonia from dyskinesia may be particularly difficult and physicians should be cautious about the potential for misdiagnosis. Tardive dystonia occurs more commonly in young men, while TD occurs more frequently in elderly patients and women.[36] Similar to TD, antipsychotic-induced rabbit syndrome tends to present after months to years of antipsychotic treatment and involves repetitive motions of the mouth or lips; however, it can be distinguished from TD by the lack of involvement of the tongue.[48]

A timely and accurate diagnosis is critical to initiating appropriate management strategies. Clinical management of movement disorders varies and may negatively impact TD if misdiagnosed. For example, parkinsonism is often treated with anticholinergic agents, which may worsen TD.[45] Caregivers are often the first to identify symptoms of TD, as patients may not notice or complain of mild symptoms.[46] This highlights the importance of proactive screening by clinicians. Patients with TD may experience many impairments, including aspiration, difficulty in chewing, increased fall risk, gait disorders, eating disorders, impairments in fine motor skills and difficulty in eating, dressing, bathing, using the restroom and sleeping (Figure 1).[26,50] Even if patients do not complain of symptoms, quality of life may be negatively impacted. Severity of TD is negatively associated with quality of life[51,52] and patients with TD have a significantly worse health-related quality of life and social withdrawal compared with similar patients without TD.[51] Notably, among patients with at least one psychiatric disorder who have three or more months of lifetime antipsychotic exposure, those with TD have lower rates of employment than those without.[53] In addition, patients may experience difficulties in carrying out daily activities necessary for independent living because of their symptoms.[54]

Risk factors for TD

Medications with known or suspected association with drug-induced TD include DRBAs (FGAs, SGAs and some antiemetics), as well as antidepressants [selective serotonin reuptake inhibitors

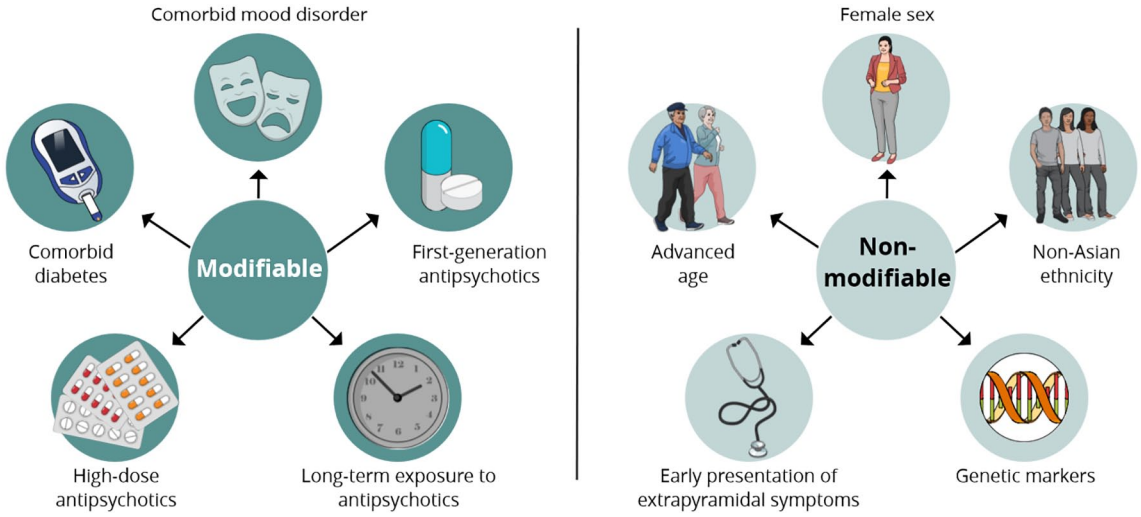


Figure 2. Risk factors for development of drug-induced tardive dyskinesia.

(SSRIs) and tricyclic antidepressants].[1,55,56] It should be noted that the evidence for the association of antidepressants with risk of developing TD is debated and may be because these agents unmask symptoms of TD that are caused by concomitant DRBA therapy.[55] Although the risk of TD is thought to be lower in patients treated with SGAs *versus* FGAs, the use of SGAs has been increasing in recent years (including off-label indications and prescriptions for mood disorders, anxiety and sleep disorders, among others) and the incidence of TD is also expected to increase.[36,57]

Risk factors for developing TD, both modifiable and non-modifiable, are illustrated in Figure 2. Age plays a role in risk, as adults have a higher risk than children, and elderly patients have the highest risk.[7,26,58–61] Initiating antipsychotics later in life (in the fifth decade or later)[61] and late-onset psychosis ($\geq$45 years of age)[62] are also associated with a greater risk of developing TD. TD is more common in women,[4,19,63] with a global study reporting an overall prevalence of 24.2% among nearly 40,000 patients with psychiatric disorders, whereas the sex-stratified prevalence was 26.6% for women and 21.6% for men.[64] Severity of TD was also reported to be greater in women than in men. Ethnicity also plays a role in TD risk, with non-Asians having a higher risk than Asians[19] and African Americans having a higher risk than other racial groups.[63]

The risk of developing TD increases with an increased cumulative duration of antipsychotic treatment.[61] For FGAs, a meta-analysis of older patients reported that the incidence estimates for probable TD were 23%, 42% and 57% after 1, 2 and 3 years of use, respectively.[65] While the risk of developing TD is lower overall for SGAs *versus* FGAs,[65] patients taking SGAs can develop TD and the incidence increases over time. A study in antipsychotic-naïve elderly patients evaluating the use of two SGAs over time reported TD incidence rates of 6.7% and 11.1% after 1 and 2 years with olanzapine treatment, and 5.3% and 7.2% with risperidone, respectively.[63] Higher cumulative exposure was also found to be associated with TD in paediatric patients taking SGAs.[66,67] For the majority of pharmacological treatments, higher doses tend to increase the risk of most adverse drug reactions;[68] this is also reported to be the case with antipsychotics.[46,69] Interestingly, a recent retrospective data analysis reported an increased risk of TD with a dose equivalent to $\leq$100 mg/day chlorpromazine but not with a dose equivalent to $>$100 mg/day;[70] this could be attributed to the increased dose of antipsychotic masking the symptoms of TD.[46]

Diabetes mellitus has been suggested as an independent risk factor for TD,[70–72] although other studies have failed to corroborate this association.[61,73,74] The link between diabetes and TD is influenced by certain treatments for symptoms of diabetes, which are known to increase the risk of TD (e.g. metoclopramide).[19,75,76]

The presence of mood disorders has been identified as a risk factor for developing TD;[77,78] however, these findings were based on older studies with FGAs and/or high doses.[19] There is a need to evaluate SGAs and lower-dose treatment

regimens in patients with mood disorders.[19] A meta-analysis of prospective studies that included patients with schizophrenia reported that early presentation of extrapyramidal symptoms was found to be a risk factor.[79]

Several genetic risk factors have also been reported; it is hoped that such findings can eventually be translated to clinical practice and lead to individualised antipsychotic treatment.[80–82] A large genome-wide study found that single-nucleotide polymorphisms (SNPs) in *TNFRSF1B* (TNF receptor superfamily member 1B) and *CALCOCO1* (calcium-binding and coiled-coil domain-containing protein 1) conferred a three-fold increase in TD risk, independent of other clinical risk factors.[80] A genome-wide association analysis of Japanese patients with schizophrenia identified an association of an SNP in the *HSPG2* (heparan sulphate proteoglycan 2, perlecan) gene.[83,84] This risk allele was associated with higher expression of *HSPG2* in the prefrontal cortex and subsequent studies in mice support an association for higher *HSPG2* expression and increased TD susceptibility.[84] A meta-analysis evaluating the effects of the *BDNF* (brain-derived neurotropic factor) gene Val66Met polymorphism on the AIMS score and TD incidence reported that the polymorphism was associated with a significantly higher AIMS score and a numerically higher incidence of TD in studies that included Caucasian patients.[85] There was no association between the polymorphism and AIMS scores or TD incidence in Asians or across all patients included in the analysis. While some studies have reported an association with TD for SNPs in the following genes: *DRD2* (dopamine 2 receptor), *DRD3* (dopamine 3 receptor),[86,87] *VMAT2* (vesicular monoamine transporter 2),[88] *HTR2A* (serotonin 2A receptor), *HTR2 C* (serotonin 2 C receptor), *SOD2* (manganese superoxide dismutase), *DPP6* (dipeptidyl peptidase-lid protein-6), *MTNR1A* (melatonin receptor 1A), *PIP5K2A* (phosphatidylinositol-4-phosphate 5-kinase IIα) and *CNR1* (cannabinoid receptor 1), more studies are needed to confirm or refute these findings.[89,90]

The influence of smoking, alcohol and substance abuse on risk of TD remains somewhat controversial, as some studies have reported an increased risk whereas others have failed to find any association. In one study, the degree of smoking was correlated with TD severity,[91] and another study found that alcohol use was similarly associated with increased TD severity.[92] A retrospective analysis of patients with TD noted a correlation between substance abuse and TD;[93] however, a newer study analysing modifiable risk factors including smoking, alcohol and substance abuse or addiction found no such association.[94] Finally, organic brain damage has been suggested as a risk factor for TD and respiratory dyskinesia, although the evidence for this is limited.[95]

Overall, the most important of these risk factors appear to be cumulative DRBA exposure and advanced age.[46] While many of the identified risk factors are non-modifiable, those that are modifiable represent an opportunity to mitigate risk. Clinicians can work with patients to improve modifiable patient factors such as working to prevent or control type 2 diabetes.[19,46] Additional approaches may include preferentially treating with SGAs *versus* FGAs and using DRBAs only when clearly indicated and minimising the dose and duration of exposure.[19,46]

Clinical situation in Japan

Various epidemiological studies in Japan have estimated antipsychotic polypharmacy rates in adult patients in Japan to be as low as 15%[96] or as high as 57%;[97] the variation in estimates may be due to differences in study design and how data were collected (e.g. cross-sectional *versus* longitudinal or type of claims database used). Outpatient *versus* inpatient status also plays a large role, as hospitalised patients are likely to have more severe disease that may be more likely to necessitate polypharmacy.[98] Nevertheless, it is broadly accepted that antipsychotic polypharmacy is more prevalent in Japan compared with other countries,[99,100] although in recent years polypharmacy and high-dose antipsychotic prescriptions have tended to decrease somewhat.[96,100] The most commonly prescribed antipsychotics in Japan include olanzapine, risperidone, aripiprazole, quetiapine and blonanserin; and elderly patients (age 60 years and above) tend to be prescribed lower doses than non-elderly adults.[98] SGAs are generally preferred over FGAs.[96,98,101]

A recent study investigating anticholinergic use among patients with schizophrenia in Japan revealed that concomitant anticholinergic prescription rates varied considerably by hospital.[102] In that study, the overall anticholinergic prescription rate was 30.5%, yet the rate ranged from 0 to 66.7% among all hospitals included in the study. Patients prescribed high doses of antipsychotics or combinations of antipsychotics were more

likely to be prescribed an anticholinergic, as were patients who received FGAs.

As has been the case overseas, some antipsychotics have been used for treatment of mood disorders in Japan. Anecdotal evidence has also suggested that antipsychotics may be prescribed to patients with co-diagnoses of dementia and epilepsy, but who may not actually be suffering from schizophrenia.[103] An administrative database study of drug use among patients in Japan diagnosed with schizophrenia suggested that a diagnosis of schizophrenia may be recorded to allow a prescription for antipsychotics, which would otherwise be considered off-label.[103] Therefore, the use of antipsychotics is likely to continue to expand and the overall incidence of TD is likely to increase.[104]

The burden of TD affects not only the patients themselves, but extends to their caregivers, as described in the RE-KINECT study, in which caregivers reported that the TD symptoms of the patient in their care impacted their own ability to continue usual activities (50.0%), be productive (58.3%), socialise (55.6%) and take care of themselves (50.0%).[53] To date, there are no Japanese studies that specifically investigate TD caregiver burden, but it is reasonable to expect that caregivers in Japan face similar issues.

Prevention of TD is important, as it may become chronic or irreversible in up to 50% of patients.[15,16,105,106] However, if detected early, it may be possible to halt the progress of TD in some patients by discontinuation or dose reduction of antipsychotics.[105] The risk of TD may also be reduced if alternative treatments are chosen when early dyskinesia is identified.[36]

Consensus recommendations for monitoring strategies for TD

As noted previously, literature describing the status of TD in Japan is limited; therefore, we have the following recommendations to address this gap. In our experience, some patients are not greatly troubled by their TD symptoms; however, those with stable psychiatric symptoms are particularly concerned about their outward appearance and how this may affect their employment or social acceptance, even if their symptoms are mild. Treatment decisions for TD should, therefore, focus foremost on patient needs. TD symptoms have a very broad spectrum of severity, and physicians should consider patients' subjective evaluation of their symptoms when deciding how to treat. The benefits of early treatment must be made clear to patients and caregivers because TD is often irreversible, and without early treatment, patients are at risk of worsening symptoms that will become burdensome.

Caregivers also play an important role in the diagnosis and treatment of TD. Physicians in Japan may have the impression that patients with TD rarely complain of symptoms unless they are severe, and that caregivers are more likely to notice subtle symptoms. In addition, caregivers have the substantial burden to constantly monitor for potentially life-threatening symptoms such as dyspnoea and dysphagia, as these symptoms can lead to fatal outcomes. For this reason, we recommend that the needs of caregivers also be considered when determining TD treatment options.

It is our opinion that although many Japanese physicians are aware that TD is a side effect of antipsychotics, they remain reluctant to diagnose TD. This might be because TD is usually irreversible, there are limited treatment options in Japan, and there is no effective cure at this time. Furthermore, physicians in Japan who have not been involved in clinical trials for TD therapeutics may not be familiar with TD and may require training in use of the AIMS or DIEPSS. To improve TD diagnosis and awareness in daily clinical practice in Japan, we believe that additional tools are needed to facilitate a full understanding of TD, and to recognise the symptoms and accurately determine severity. Short (i.e. 5-min) consultations generally do not provide enough time for the observation of TD symptoms; therefore, we recommend that patients be observed for at least 15–30 min.

Because of the increased use of antipsychotic medications for mood disorders in Japan in recent years, we think that physicians who treat patients with mood disorders need to be aware of TD. Physicians should also be aware of the current perception that SGAs are less likely than FGAs to cause TD, yet should remain vigilant in monitoring for signs of TD regardless of the type of antipsychotics prescribed. Many aspects of our recommendations are in line with the recommendations of US consensus panels published in 2020[107] and 2021.[108] These include the importance of frequent monitoring for TD and an understanding that patients may not be aware of

their TD symptoms. The importance of involving caregivers and family members in discussions around TD, such as gathering information regarding symptoms and deciding on when and how to treat, was also noted by both US consensus panels. In addition, assessment of the impact of TD on a patient's life was emphasised and five key evaluation areas were listed, which included social, physical, vocational, psychological and psychiatric. Both US groups recommended tailoring the treatment plan to each individual's daily life and abilities. To improve the current situation in Japan, it is important for patients to be informed that TD is a potential side effect of antipsychotics so that they can effectively monitor themselves for symptoms.

We also recommend avoiding the overuse of antipsychotics as a key strategy to prevent TD occurrence. Regarding early detection, we advise that physicians remain vigilant and observe their patients carefully for signs of TD development. There is a large variation in reports of TD awareness among psychiatric patients, with one study of psychiatric outpatients in the United States suggesting only 25% of patients were unaware of possible TD symptoms,[109] whereas another study conducted among psychiatric inpatients in Singapore reported that 67% of patients with TD were unaware of their abnormal movements.[110] Early detection is crucial for effective treatment of TD, and risk may be further mitigated by appropriate and timely selection of alternative treatments for the underlying psychiatric disease at the first signs of extrapyramidal symptoms.

Concluding summary

Given that effective new therapeutic agents have emerged and more treatment options are becoming available, we think it is important to achieve a high level of awareness of TD among physicians, and to ensure that patients are proactively monitored for signs of TD.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Yasuhiro Mori: Conceptualization; Methodology; Writing – original draft; Writing – review & editing.

Hiroyoshi Takeuchi: Conceptualization; Writing – review & editing.

Yuichiro Tsutsumi: Conceptualization; Writing – review & editing.

Acknowledgements

The authors thank Sarah Bubeck, PhD, of Edanz, Japan, for medical writing assistance and publication support, which was funded by Mitsubishi Tanabe Pharma Corporation, and Dr Koichiro Watanabe for facilitating the roundtable discussion. The authors have authorised the submission of this article *via* Edanz and have approved the funding and conflict of interest statements.

Funding

The authors disclosed receipt of the following financial support for the research, authorship and/or publication of this article: This work was supported by Mitsubishi Tanabe Pharma Corporation, who also reviewed the content for medical and scientific accuracy as well as intellectual property considerations.

Competing interests

The authors declared the following potential conflicts of interest with respect to the research, authorship and/or publication of this article: HT reports research grants from Daiichi Sankyo and Novartis Pharma; speaker's fees from EA Pharma, Kyowa, Janssen, Lundbeck, Meiji Seika Pharma, Mochida, Otsuka, Sumitomo Pharma, Takeda, and Yoshitomiyakuhin; and advisory board fees from Janssen, Mitsubishi Tanabe Pharma, and Sumitomo Pharma. YM reports advisory board fees from Mitsubishi Tanabe Pharma. YT reports speaker's fees from Janssen, Lundbeck, Meiji Seika Pharma, Mitsubishi Tanabe Pharma, Sumitomo Pharma, and Takeda; and advisory board fees from Mitsubishi Tanabe Pharma.

Availability of data and materials

Not applicable.

ORCID iDs

Yasuhiro Mori https://orcid.org/0000-0002-5066-2390

Hiroyoshi Takeuchi https://orcid.org/0000-0002-8844-4786

Supplemental material

Supplemental material for this article is available online.

References

1. Waln O and Jankovic J. An update on tardive dyskinesia: from phenomenology to treatment. *Tremor Other Hyperkinet Mov (N Y)* 2013; 3: tre-03-161-4138-1.
2. Cornett EM, Novitch M, Kaye AD, *et al.* Medication-induced tardive dyskinesia: a review and update. *Ochsner J* 2017; 17: 162–174.
3. American Psychiatric Association. *Diagnostic and statistical manual for mental disorders*. 5th ed. Arlington, VA: American Psychiatric Association, 2013.
4. Correll CU, Leucht S and Kane JM. Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. *Am J Psychiatry* 2004; 161: 414–425.
5. Kane JM. Tardive dyskinesia rates with atypical antipsychotics in adults: prevalence and incidence. *J Clin Psychiatry* 2004; 65(Suppl. 9): 16–20.
6. Tarsy D and Baldessarini RJ. Epidemiology of tardive dyskinesia: is risk declining with modern antipsychotics. *Mov Disord* 2006; 21: 589–598.
7. Correll CU and Schenk EM. Tardive dyskinesia and new antipsychotics. *Curr Opin Psychiatry* 2008; 21: 151–156.
8. Carbon M, Kane JM, Leucht S, *et al.* Tardive dyskinesia risk with first- and second-generation antipsychotics in comparative randomized controlled trials: a meta-analysis. *World Psych* 2018; 17: 330–340.
9. Cloud LJ, Zutshi D and Factor SA. Tardive dyskinesia: therapeutic options for an increasingly common disorder. *Neurotherapeutics* 2014; 11: 166–176.
10. Revuelta GJ, Cloud LJ, Aia PG, *et al. Tardive dyskinesias*. Chichester: Wiley-Blackwell, 2012, pp. 331–352.
11. Lerner PP, Miodownik C and Lerner V. Tardive dyskinesia (syndrome): current concept and modern approaches to its management. *Psychiatry Clin Neurosci* 2015; 69: 321–334.
12. Chiu HF, Chung DW, Wing YK, *et al.* Life-threatening tardive dyskinesia. *Br J Clin Pract* 1996; 50: 175–176.
13. Samie MR, Dannenhoffer MA and Rozek S. Life-threatening tardive dyskinesia caused by metoclopramide. *Mov Disord* 1987; 2: 125–129.
14. Savitt D and Jankovic J. Tardive syndromes. *J Neurol Sci* 2018; 389: 35–42.
15. Muench J and Hamer AM. Adverse effects of antipsychotic medications. *Am Fam Physician* 2010; 81: 617–622.
16. Zutshi D, Cloud LJ and Factor SA. Tardive syndromes are rarely reversible after discontinuing dopamine receptor blocking agents: experience from a university-based movement disorder clinic. *Tremor Other Hyperkinet Mov (N Y)* 2014; 4: 266.
17. Desapriya EB and Nobutada I. Stigma of mental illness in Japan. *Lancet* 2002; 359: 1866.
18. Kasahara-Kiritani M, Matoba T, Kikuzawa S, *et al.* Public perceptions toward mental illness in Japan. *Asian J Psychiatry* 2018; 35: 55–60.
19. Solmi M, Pigato G, Kane JM, *et al.* Clinical risk factors for the development of tardive dyskinesia. *J Neurol Sci* 2018; 389: 21–27.
20. Carbon M, Hsieh CH, Kane JM, *et al.* Tardive dyskinesia prevalence in the period of second-generation antipsychotic use: a meta-analysis. *J Clin Psychiatry* 2017; 78: e264–e278.
21. Mentzel TQ, van der Snoek R, Lieverse R, *et al.* Clozapine monotherapy as a treatment for antipsychotic-induced tardive dyskinesia: a meta-analysis. *J Clin Psychiatry* 2018; 79: 17r11852.
22. Novick D, Haro JM, Bertsch J, *et al.* Incidence of extrapyramidal symptoms and tardive dyskinesia in schizophrenia: thirty-six-month results from the European schizophrenia outpatient health outcomes study. *J Clin Psychopharmacol* 2010; 30: 531–540.
23. Inagaki N, Sato H, Inada K, *et al.* Safety of antipsychotic pharmacotherapy for schizophrenia: a review of clinical trials and post-marketing surveillance studies conducted in Japan. *Jpn J Clin Psychopharmacol* 2021; 24: 1153–1169.
24. Inada T and Yagi G. Current topics in tardive dyskinesia in Japan. *Psychiatry Clin Neurosci* 1995; 49: 239–244.

25. Xiang YT, Wang CY, Si TM, *et al.* Tardive dyskinesia in the treatment of schizophrenia: the findings of the Research on Asian Psychotropic Prescription Pattern (REAP) survey (2001–2009). *Int J Clin Pharmacol Ther* 2011; 49: 382–377.

26. Jain R and Correll CU. Tardive dyskinesia: recognition, patient assessment, and differential diagnosis. *J Clin Psychiatry* 2018; 79: nu17034ah1c.

27. Elkurd MT and Bahroo L. Keeping up with the clinical advances: tardive dyskinesia. *CNS Spectr* 2019; 24(S1): 70–81.

28. Charlson FJ, Ferrari AJ, Santomauro DF, *et al.* Global epidemiology and burden of schizophrenia: findings from the Global Burden of Disease Study 2016. *Schizophr Bull* 2018; 44: 1195–1203.

29. Bleuler E. *Dementia praecox or the group of schizophrenia*. New York: International University Press, 1950.

30. Kraepelin E. *Dementia praecox and Paraphrenia*. New York: Robert E. Krieger, 1919.

31. Reiter P. Extrapyramidal motor-disturbances in dementia praecox. *Acta Psychiatr Neurol Scand* 1926; 1: 287–309.

32. Koning JP, Tenback DE, van Os J, *et al.* Dyskinesia and parkinsonism in antipsychotic-naive patients with schizophrenia, first-degree relatives and healthy controls: a meta-analysis. *Schizophr Bull* 2010; 36: 723–731.

33. Dilks S, Xavier RM, Kelly C, *et al.* Implications of antipsychotic use: antipsychotic-induced movement disorders, with a focus on tardive dyskinesia. *Nurs Clin North Am* 2019; 54: 595–608.

34. Anderson EP and Freeman EB. Recognition of movement disorders: extrapyramidal side effects and tardive dyskinesia. Would you recognize them if you see them? *Practical Gastroenterol* 2004; 28: 14–26.

35. Paulson GW. Historical comments on tardive dyskinesia: a neurologist's perspective. *J Clin Psychiatry* 2005; 66: 260–264.

36. Correll CU, Kane JM and Citrome LL. Epidemiology, prevention, and assessment of tardive dyskinesia and advances in treatment. *J Clin Psychiatry* 2017; 78: 1136–1147.

37. Schooler NR and Kane JM. Research diagnoses for tardive dyskinesia. *Arch Gen Psychiatry* 1982; 39: 486–487.

38. Gopal S, Xu H, Bossie C, *et al.* Incidence of tardive dyskinesia: a comparison of long-acting injectable and oral paliperidone clinical trial databases. *Int J Clin Pract* 2014; 68: 1514–1522.

39. Kane JM, Correll CU, Nierenberg AA, *et al.* Revisiting the abnormal involuntary movement scale: proceedings from the tardive dyskinesia assessment workshop. *J Clin Psychiatry* 2018; 79: 17cs11959.

40. Guy W. *ECDEU assessment manual for psychopharmacology*. Washington, DC: US Department of Health, Education, and Welfare, 1976.

41. Inada T, Beasley CM Jr, Tanaka Y, *et al.* Extrapyramidal symptom profiles assessed with the Drug-Induced Extrapyramidal Symptom Scale: comparison with Western scales in the clinical double-blind studies of schizophrenic patients treated with either olanzapine or haloperidol. *Int Clin Psychopharmacol* 2003; 18: 39–48.

42. Inada T. *DIEPSS: a second-generation rating scale for antipsychotic-induced extrapyramidal symptoms: Drug-Induced Extrapyramidal Symptoms Scale*. Tokyo, Japan: Seiwa Shoten Publishers, 2009.

43. Inada T, Yagi G and Miura S. Extrapyramidal symptom profiles in Japanese patients with schizophrenia treated with olanzapine or haloperidol. *Schizophr Res* 2002; 57: 227–238.

44. Hauser RA, Meyer JM, Factor SA, *et al.* Differentiating tardive dyskinesia: a video-based review of antipsychotic-induced movement disorders in clinical practice. *CNS Spectr* 2022; 27: 208–217.

45. Ward KM and Citrome L. Antipsychotic-related movement disorders: drug-induced Parkinsonism vs. tardive dyskinesia-key differences in pathophysiology and clinical management. *Neurol Ther* 2018; 7: 233–248.

46. Citrome L and Saklad SR. Revisiting tardive dyskinesia: focusing on the basics of identification and treatment. *J Clin Psychiatry* 2020; 81: TV18059AH18053C.

47. Caroff SN, Hurford I, Lybrand J, *et al.* Movement disorders induced by antipsychotic drugs: implications of the CATIE schizophrenia trial. *Neurol Clin* 2011; 29: 127–148, viii.

48. Schwartz M and Hocherman S. Antipsychotic-induced rabbit syndrome: epidemiology, management and pathophysiology. *CNS Drugs* 2004; 18: 213–220.

49. Tarsy D. Neuroleptic-induced extrapyramidal reactions: classification, description, and diagnosis. *Clin Neuropharmacol* 1983; 6(Suppl. 1): S9–S26.

50. Horiguchi J. Recent findings and clinical subjects of tardive dyskinesia. *Seishin Igaku* 2021; 63: 247–259.

51. 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: 3303–3312.
52. Othman Z, Ghazali M, Razak AA, *et al.* Severity of tardive dyskinesia and negative symptoms are associated with poor quality of life in schizophrenia patients. *Int Med J* 1994; 20: 667–680.
53. Cutler AJ, Caroff SN, Tanner CM, *et al.* Caregiver-reported burden in RE-KINECT: data from a prospective real-world tardive dyskinesia screening study. *J Am Psychiatr Nurses Assoc*. Epub ahead of print 22 June 2021. DOI: 10.1177/10783903211023565.
54. Strassnig M, Rosenfeld A and Harvey PD. Tardive dyskinesia: motor system impairments, cognition and everyday functioning. *CNS Spectr* 2018; 23: 370–377.
55. D'Abreu A and Friedman JH. Tardive dyskinesia-like syndrome due to drugs that do not block dopamine receptors: rare or non-existent: literature review. *Tremor Other Hyperkinet Mov (N Y)* 2018; 8: 570.
56. Revet A, Montastruc F, Roussin A, *et al.* Antidepressants and movement disorders: a postmarketing study in the world pharmacovigilance database. *BMC Psychiatry* 2020; 20: 308.
57. Alexander GC, Gallagher SA, Mascola A, *et al.* Increasing off-label use of antipsychotic medications in the United States, 1995-2008. *Pharmacoepidemiol Drug Saf* 2011; 20: 177–184.
58. Goldberg RJ. Tardive dyskinesia in elderly patients: an update. *J Am Med Dir Assoc* 2002; 3: 152–161.
59. Ragheb MM and Goldberg RJ. Tardive dyskinesia in geriatric patients. *Aging Health* 2006; 2: 833–849.
60. Kane JM. Tardive dyskinesia in elderly patients: an update. *Psychiatric Annals* 2002; 32: 233–236.
61. Woerner MG, Alvir JM, Saltz BL, *et al.* Prospective study of tardive dyskinesia in the elderly: rates and risk factors. *Am J Psychiatry* 1998; 155: 1521–1528.
62. Yassa R, Nair V and Schwartz G. Early versus late onset psychosis and tardive dyskinesia. *Biol Psychiatry* 1986; 21: 1291–1297.
63. Woerner MG, Correll CU, Alvir JM, *et al.* Incidence of tardive dyskinesia with risperidone or olanzapine in the elderly: results from a 2-year, prospective study in antipsychotic-naive patients. *Neuropsychopharmacology* 2011; 36: 1738–1746.
64. Yassa R and Jeste DV. Gender differences in tardive dyskinesia: a critical review of the literature. *Schizophr Bull* 1992; 18: 701–715.
65. O'Brien A. Comparing the risk of tardive dyskinesia in older adults with first-generation and second-generation antipsychotics: a systematic review and meta-analysis. *Int J Geriatr Psychiatry* 2016; 31: 683–693.
66. Garcia-Amador M, Merchan-Naranjo J, Tapia C, *et al.* Neurological adverse effects of antipsychotics in children and adolescents. *J Clin Psychopharmacol* 2015; 35: 686–693.
67. Pisano S, Catone G, Veltri S, *et al.* Update on the safety of second generation antipsychotics in youths: a call for collaboration among paediatricians and child psychiatrists. *Ital J Pediatr* 2016; 42: 51.
68. Haddad PM and Sharma SG. Adverse effects of atypical antipsychotics: differential risk and clinical implications. *CNS Drugs* 2007; 21: 911–936.
69. Yoshida K and Takeuchi H. Dose-dependent effects of antipsychotics on efficacy and adverse effects in schizophrenia. *Behav Brain Res* 2021; 402: 113098.
70. Patterson-Lomba O, Ayyagari R and Carroll B. Risk assessment and prediction of TD incidence in psychiatric patients taking concomitant antipsychotics: a retrospective data analysis. *BMC Neurol* 2019; 19: 174.
71. Woerner MG, Saltz BL, Kane JM, *et al.* Diabetes and development of tardive dyskinesia. *Am J Psychiatry* 1993; 150: 966–968.
72. Ganzini L, Casey DE, Hoffman WF, *et al.* Tardive dyskinesia and diabetes mellitus. *Psychopharmacol Bull* 1992; 28: 281–286.
73. Raja M and Azzoni A. Diabetes is not a risk factor for tardive dyskinesia: a retrospective observational study. *Hum Psychopharmacol* 2002; 17: 61–63.
74. Levy E, Margolese HC, Annable L, *et al.* Diabetes, tardive dyskinesia, parkinsonism, and akathisia in schizophrenia: a retrospective study applying 1998 diabetes health care guidelines to antipsychotic use. *Can J Psychiatry* 2004; 49: 398–402.
75. Rao AS and Camilleri M. Review article: metoclopramide and tardive dyskinesia. *Aliment Pharmacol Ther* 2010; 31: 11–19.
76. Al-Saffar A, Lennernas H and Hellstrom PM. Gastroparesis, metoclopramide, and tardive

dyskinesia: risk revisited. *Neurogastroenterol Motil* 2019; 31: e13617.

77. Yassa R, Nair V and Schwartz G. Tardive dyskinesia and the primary psychiatric diagnosis. *Psychosomatics* 1984; 25: 135–138.

78. Yassa R and Schwartz G. Depression as a predictor in the development of tardive dyskinesia. *Biol Psychiatry* 1984; 19: 441–444.

79. Tenback DE, van Harten PN and van Os J. Non-therapeutic risk factors for onset of tardive dyskinesia in schizophrenia: a meta-analysis. *Mov Disord* 2009; 24: 2309–2315.

80. Lim K, Lam M, Zai C, *et al.* Genome wide study of tardive dyskinesia in schizophrenia. *Transl Psychiatry* 2021; 11: 351.

81. Thelma B, Srivastava V and Tiwari AK. Genetic underpinnings of tardive dyskinesia: passing the baton to pharmacogenetics. *Pharmacogenomics* 2008; 9: 1285–1306.

82. Ohmori O, Shinkai T, Hori H, *et al.* A perspective on molecular genetic studies of tardive dyskinesia: one clue for individualized antipsychotic drug therapy. *Prog Neuropsychopharmacol Biol Psychiatry* 2003; 27: 581–586.

83. Arinami T and Inada T. [Genome-wide association analyses for neuroleptic-induced tardive dyskinesia]. *Nihon Shinkei Seishin Yakurigaku Zasshi* 2011; 31: 155–162.

84. Syu A, Ishiguro H, Inada T, *et al.* Association of the HSPG2 gene with neuroleptic-induced tardive dyskinesia. *Neuropsychopharmacology* 2010; 35: 1155–1164.

85. Miura I, Zhang JP, Nitta M, *et al.* BDNF Val66Met polymorphism and antipsychotic-induced tardive dyskinesia occurrence and severity: a meta-analysis. *Schizophr Res* 2014; 152: 365–372.

86. Bakker PR, van Harten PN and van Os J. Antipsychotic-induced tardive dyskinesia and the Ser9Gly polymorphism in the DRD3 gene: a meta analysis. *Schizophr Res* 2006; 83: 185–192.

87. Rizos EN, Siafakas N, Katsantoni E, *et al.* Association of the dopamine D3 receptor Ser9Gly and of the serotonin 2C receptor gene polymorphisms with tardive dyskinesia in Greeks with chronic schizophrenic disorder. *Psychiatr Genet* 2009; 19: 106–107.

88. Zai CC, Tiwari AK, Mazzoco M, *et al.* Association study of the vesicular monoamine transporter gene SLC18A2 with tardive dyskinesia. *J Psychiatr Res* 2013; 47: 1760–1765.

89. Zai CC, Maes MS, Tiwari AK, *et al.* Genetics of tardive dyskinesia: promising leads and ways forward. *J Neurol Sci* 2018; 389: 28–34.

90. Lanning RK, Zai CC and Muller DJ. Pharmacogenetics of tardive dyskinesia: an updated review of the literature. *Pharmacogenomics* 2016; 17: 1339–1351.

91. Diehl A, Reinhard I, Schmitt A, *et al.* Does the degree of smoking effect the severity of tardive dyskinesia? A longitudinal clinical trial. *Eur Psychiatry* 2009; 24: 33–40.

92. Dixon L, Weiden PJ, Haas G, *et al.* Increased tardive dyskinesia in alcohol-abusing schizophrenic patients. *Compr Psychiatry* 1992; 33: 121–122

93. Bailey LG, Maxwell S and Brandabur MM. Substance abuse as a risk factor for tardive dyskinesia: a retrospective analysis of 1,027 patients. *Psychopharmacol Bull* 1997; 33: 177–181.

94. Vardar MK, Ceylan ME and Ünsalver B. Assessment of risk factors for tardive dyskinesia. *Psychopharmacol Bull* 2020; 50: 36–46.

95. Hayashi T, Nishikawa T, Koga I, *et al.* Prevalence of and risk factors for respiratory dyskinesia. *Clin Neuropharmacol* 1996; 19: 390–398.

96. Kochi K, Sato I, Nishiyama C, *et al.* Trends in antipsychotic prescriptions for Japanese outpatients during 2006-2012: a descriptive epidemiological study. *Pharmacoepidemiol Drug Saf* 2017; 26: 642–656.

97. Dong M, Zeng LN, Zhang Q, *et al.* Prescription of antipsychotic and concomitant medications for adult Asian schizophrenia patients: findings of the 2016 Research on Asian Psychotropic Prescription Patterns (REAP) survey. *Asian J Psychiatr* 2019; 45: 74–80.

98. Hashimoto N, Yasui-Furukori N, Hasegawa N, *et al.* Characteristics of discharge prescriptions for patients with schizophrenia or major depressive disorder: real-world evidence from the Effectiveness of Guidelines for Dissemination and Education (EGUIDE) psychiatric treatment project. *Asian J Psychiatr* 2021; 63: 102744.

99. Ichihashi K, Hori H, Hasegawa N, *et al.* Prescription patterns in patients with schizophrenia in Japan: first-quality indicator data from the survey of 'Effectiveness of Guidelines for Dissemination and Education in psychiatric treatment (EGUIDE)' project. *Neuropsychopharmacol Rep* 2020; 40: 281–286.

100. Yang SY, Chen LY, Najoan E, *et al.* Polypharmacy and psychotropic drug loading in patients with schizophrenia in Asian countries: fourth survey of research on Asian prescription patterns on antipsychotics. *Psychiatry Clin Neurosci* 2018; 72: 572–579.

101. Shinfuku N. Research on Asian Psychotropic Prescription Pattern (REAP). *Jpn Bull Soc Psychiat* 2014; 23: 90–103.

102. Hori H, Yasui-Furukori N, Hasegawa N, *et al.* Prescription of anticholinergic drugs in patients with schizophrenia: analysis of antipsychotic prescription patterns and hospital characteristics. *Front Psychiatry* 2022; 13: 823826.

103. Cheung S, Hamuro Y, Mahlich J, *et al.* Drug utilization of Japanese patients diagnosed with schizophrenia: an administrative database analysis. *Clin Drug Investig* 2017; 37: 559–569.

104. Kanba S, Kato T, Terao T, *et al.* Guideline for treatment of bipolar disorder by the Japanese society of mood disorders, 2012. *Psychiatry Clin Neurosci* 2013; 67: 285–300.

105. Citrome L, Dufresne R and Dyrud JM. Tardive dyskinesia: minimizing risk and improving outcomes in schizophrenia and other disorders. *Am J Manag Care* 2007; 12: 1–12.

106. Glazer WM. Expected incidence of tardive dyskinesia associated with atypical antipsychotics. *J Clin Psychiatry* 2000; 61(Suppl. 4): 21–26.

107. 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: 19cs12983.

108. Jackson R, Brams MN, Citrome L, *et al.* Assessment of the impact of tardive dyskinesia in clinical practice: consensus panel recommendations. *Neuropsychiatr Dis Treat* 2021; 17: 1589–1597.

109. 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: 259–268.

110. Chong SA, Remington G, Mahendran R, *et al.* Awareness of tardive dyskinesia in Asian patients with schizophrenia. *J Clin Psychopharmacol* 2001; 21: 235–237.