Tardive Dyskinesia Associated with Atypical Antipsychotics

CNS Drugs (2018) 32:135–147
https://doi.org/10.1007/s40263-018-0494-8

REVIEW ARTICLE

Tardive Dyskinesia Associated with Atypical Antipsychotics: Prevalence, Mechanisms and Management Strategies

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Published online: 9 February 2018

Abstract All antipsychotics, including the atypical antipsychotics (AAPs), may cause tardive dyskinesia (TD), a potentially irreversible movement disorder, the pathophysiology of which is currently unknown. The prevention and treatment of TD remain major challenges for clinicians. We conducted a PubMed search to review the prevalence and etiology of and management strategies for TD associated with AAPs. TD prevalence rates varied substantially between studies, with an estimated prevalence of around 20% in patients using AAPs. The risk of TD is lower with AAPs than with typical antipsychotics (TAPs) but remains a problem because AAPs are increasingly being prescribed. Important risk factors associated with TD include the duration of antipsychotic use, age, and ethnicity other than Caucasian. Theories about the etiology of TD include supersensitivity of the dopamine receptors and oxidative stress, but other neurotransmitters and factors are probably involved. Studies concerning the management of TD have considerable methodological limitations. Thus, recommendations for the management of TD are based on a few trials and clinical experience, and no general guidelines for the management of TD can be established. The best management strategy remains prevention. Caution is required when prescribing antipsychotics, and regular screening is needed for early detection of TD. Other strategies may include reducing the AAP dosage, switching to clozapine, or administering vesicular monoamine transporter (VMAT)-2 inhibitors. In severe cases, local injections of botulinum toxin or deep brain stimulation may be considered. More clinical trials in larger samples are needed to gather valid information on the effect of interventions targeting TD.

Key Points

Tardive dyskinesia (TD) is less common in patients receiving atypical antipsychotics (AAP) than in those receiving typical antipsychotics but remains a problem.

The best management strategy remains prevention, including caution when prescribing antipsychotics and regular screening for early detection of TD.

Treatment strategies may include reduction of antipsychotic dosage, switching to clozapine, or administration of vesicular monoamine transporter (VMAT)-2 inhibitors.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40263-018-0494-8) contains supplementary material, which is available to authorized users.

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1 Introduction

Tardive dyskinesia (TD) is characterized by abnormal involuntary movements, typically manifesting as involuntary continuous orofacial movements and dyskinetic movements of the extremities or trunk [1]. TD often occurs in psychiatric patients who have been treated with antipsychotics for many years [2]. The *Diagnostic and Statistical Manual of Mental Disorders, fifth edition* (DSM-5) classifies TD as a medication-induced movement disorder that can occur after long-term—but also short-term—treatment with antipsychotics and that persists for at least 1 month after discontinuation of medication. However, dyskinesia is not exclusively related to antipsychotic use; it was described in chronic schizophrenia long before antipsychotics were invented, in drug-naïve patients with a first episode of a psychotic disorder [3–5], and in subjects at risk for psychosis [6]. In addition, motor symptoms such as TD often wax and wane during follow-up [1, 7–10]. Furthermore, TD can be caused by a range of other medications, particularly, but not exclusively, medications with dopamine (DA) receptor-blocking properties [11]. Thus, dyskinesia may be a symptom of the psychotic spectrum disorders or may be related to DA receptor-blocking agents such as antipsychotics.

Antipsychotic pharmacotherapy includes both typical antipsychotics (TAPs) and atypical antipsychotics (AAPs). Less than a decade after antipsychotics were introduced, motor side effects were being noted in approximately 40% of patients receiving them [12]. In the 1990s, a new group of antipsychotics, classed as AAPs, were introduced. The atypicality of antipsychotics was thought to be related to their pharmacological profiles. In particular, antagonism of the serotonin (5-HT)-2 receptor/dopamine-2 (D_2) receptor ratio (5-HT_2/D_2 ratio) was suggested as a predictor of extrapyramidal side effects, relevant for transient elevations in prolactin levels and treatment efficacy (the in vitro binding profiles of AAPs indicate the following hierarchy of 5-HT_{2C}/D_2 ratios: clozapine < ziprasidone < olanzapine < risperidone < aripiprazole) [13–15]. Extensive marketing and a suggested benefit regarding extrapyramidal side effects compared with older antipsychotics (TAPs) led to a substantial increase in the rate of AAP prescriptions [16]. The main reason for this high acceptance of AAPs was the reduced likelihood of inducing acute extrapyramidal side effects such as parkinsonism and akathisia [17]. Although the marketing messages claimed TD was less prevalent and had a lower incidence with AAPs than with TAPs, the evidence was not conclusive. The exception is clozapine, the most atypical AAP (classified as an AAP even though it was already on the market in the 1960s); substantial evidence indicates it is almost free of extrapyramidal side effects, apart from akathisia. However, although the risk of TD is generally agreed to be lower with clozapine than with TAPs, evidence remains that even clozapine may cause new TD or intensify existing TD [18–37] (for review, see Hazari et al. [38]). However, the decrease in TD prevalence rates with all other AAPs was much less than expected, and clinicians are cautioned not to overestimate the safety of AAPs [39].

Various risk factors, such as ethnicity other than Caucasian, a history of acute extrapyramidal side effects, advanced age, smoking, sex, organic brain injuries, and diabetes mellitus have been associated with TD [40]. Neuroleptic-induced DA supersensitivity, particularly in the nigrostriatal pathway, has been suggested as a potential mechanism underlying the condition [41], but the exact mechanism remains unclear. Importantly, TD is a potentially irreversible condition that can cause substantial disability and is thought to be associated with particularly poor outcomes [42, 43]. Moreover, TD may critically reduce compliance with potentially very effective and indispensable medication.

A range of pharmacological and non-pharmacological treatments for TD have been proposed, and the US FDA recently approved the first medications (valbenazine and deutetrabenazine) for the treatment of TD in adults. However, several aspects, including polypharmacy, challenge the identification of, quantification of risk for, study of pathophysiology of, and—most importantly—management of TD. Furthermore, the diagnosis of TD is not as straightforward as it appears. Dyskinesia can also be a symptom of the psychotic disorder itself. Likewise, the management of patients receiving multiple psychotropic substances is challenging.

The objective of this review was to give a comprehensive overview of the prevalence of and potential mechanisms for TD and to provide, based on available data and clinical experience, management strategies for TD associated with AAPs.

We conducted a PubMed search using keywords and a combined keyword search to identify the prevalence and possible mechanisms of and management strategies for AAP-associated TD. Cross-references were also checked. We restricted the search to studies published in English in the last 10 years and expanded the search's time span in case of missing or very few results. Reported results are mostly restricted to humans, non-affective disorders, and adults.

In detail, for prevalence, we used the following keywords: tardive dyskinesia, antipsychotics, neuroleptics, atypical antipsychotics, medication induced, incidence, prevalence, occurrence, and specific substances (i.e., amisulpride, clozapine, olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole). For mechanism, we used the

following keywords: tardive dyskinesia, mechanism, pathophysiology, etiology, D2 receptor, dopamine, oxidative stress, synaptic plasticity, neurotoxicity, neuroadaptive signaling, anticholinergic agents, and genetics. For management strategies, we used the following keywords: tardive dyskinesia, antipsychotics, neuroleptics, atypical antipsychotics, medication induced, prevention, treatment, vitamins, GABA agonists, benzodiazepines, anticholinergics, cholinergic, calcium channel blockers, non-antipsychotic dopaminergic, noradrenergic, antipsychotic reduction, intermittent therapy, botulin toxin, insulin, lithium, deep brain stimulation, vesicular monoamine transporter 2 inhibitors (VMAT-2 inhibitors), specific VMAT-2 inhibitors (tetrabenazine, valbenazine, deutetrabenazine), and specific antipsychotic substances.

2 Prevalence

A large body of evidence reports on the prevalence of TD, even though alternative causes of dyskinesia are typically not considered. A recent meta-analysis of 41 studies conducted between 2000 and 2015 indicated that TD is less common but continues to be a relevant problem in patients treated with AAPs [44]. In detail, Carbon et al. [44] reported a global mean prevalence of TD of 25.3% [95% confidence interval (CI) 22.7–28.1]. Rates of TD were lower with current AAP treatment (20.7%; 95% CI 16.6–25.4) than with current TAP treatment (30.0%; 95% CI 26.4–33.8). The prevalence of TD was particularly low in patients who were TAP naïve (7.2%). However, this was only the case in four of the studies included in the analysis. The results of this carefully conducted meta-analysis are widely comparable with previous reports including their own data [45, 46]. However, whether the prevalence of TD in patients receiving AAPs is truly markedly reduced remains questionable, as at least some studies did not find a lower prevalence of TD in patients receiving AAPs compared with those receiving TAPs [47, 48].

We detected two observational studies [49, 50], one case series [51], and one meta-analysis [52] assessing TD prevalence rates in adults receiving AAPs that were published between 2015 and August 2017 and were therefore not included in the aforementioned meta-analysis. The first observational study was a longitudinal study of 1120 relatively young patients (mean age 27 years) with non-affective psychosis [49]. The TD prevalence rate in this population was 4% (incidence rates 3%; persistence rates 20%). Thus, prevalence rates were much lower than reported in the aforementioned meta-analysis. These results confirm not only that TD increases with age and duration of illness but also that TD occurs in a considerable proportion of patients early in the course of the disease.

The second observational study (long-term follow-up of 8 years) [50] failed to detect differences in antipsychotic-induced movement disorders in the subgroups of patients who were treated with TAPs, AAPs, or a combination of TAPs and AAPs. In their sample of chronically ill patients, only 15.3% were free of any movement disorder. However, the sample size ($n = 72$) was small, the study focused on comparing the prevalence of comorbidities, and TD prevalence rates were not separated from those of parkinsonism. One case series followed 15 patients for approximately 2.5 years and assessed the prevalence of rebound psychosis, tolerance to antipsychotic effects, and TD before and during treatment with clozapine [51]. In four of five clozapine-naïve patients with TD, the TD disappeared following treatment with clozapine. Finally, O'Brien [52] conducted a meta-analysis to compare the risk of TD in older adults receiving TAPs or AAPs and detected a more than threefold reduction in the risk of probable TD over 1 year (23 vs. 7%, respectively). The incidence estimate of 7% for AAPs in this meta-analysis was similar to the incidence estimates of 5.2 and 5.3% in previous reports [45, 46]. These studies identified no prevalence studies reporting rates of AAP-related TD in older adults.

Questions have been raised over the validity of reports of TD prevalence. In particular, only a minority of studies comparing the prevalence of TD in patients receiving AAPs or TAPs were randomized controlled trials (RCTs). Furthermore, doses of TAPs in these studies are mostly high, which is associated with an increased risk of developing TD. Likewise, it is difficult to conclude from the available data whether TD prevalence is markedly reduced with AAPs compared with TAPs. Another important aspect is that cohorts are very likely to have been exposed to TAPs before switching to AAPs. This hampers the attribution of TD to a specific class of antipsychotic. Moreover, prevalence rates depend on the type of rating scale used and whether instrumental assessments are used to detect TD [53]. Minimal to mild TD may remain undetected in the clinical routine. For instance, the prevalence of TD was lower in the SOHO (Schizophrenia Outpatient Health Outcomes) study (9.4%), most likely because the study recorded spontaneous observations of TD instead of using specific rating scales such as the Abnormal Involuntary Movement Scale (AIMS) [54]. In addition, in most cases, it is not possible to distinguish between spontaneous or medication-induced TD, raising concerns about the "true" prevalence of medication-induced TD [9]. Finally, studies assessing incidence rates are rare. An increasing risk for TD is associated with the duration of medication and other risk factors (i.e., age, genetics, non-Caucasian ethnicity). Tenback and van Harten [40] summarized replicated risk factors for TD.

The fact that the prevalence of TD in patients receiving AAPs is not markedly reduced compared with patients receiving TAPs challenges the hypothesized mechanism of D2 receptor affinity in TD. However, while data for antipsychotic class are available, most studies do not provide specific TD rates per individual antipsychotic agent. Given the pharmacological profile of different types of AAPs (i.e., the 5-HT_2/D_2 ratio), it may still be speculated that the prevalence of TD differs between antipsychotic agents [15]. In particular, the prototypical AAP is clozapine, which reportedly has a lower frequency of acute drug-induced movement disorders. Thus, investigation of the prevalence of TD in individual AAP agents is warranted.

In summary, we conclude that the prevalence of TD in patients receiving AAPs is approximately 20%. Although TD prevalence is lower with AAPs than with TAPs, it remains a problem, even in patients who have never received a TAP [44] and in relatively young patients [49]. These numbers suggest that the implementation of standard TD screenings in all subjects treated with antipsychotics, including before the first administration, are necessary.

3 Mechanism

There is no consensus about an underlying mechanism that provokes the development of TD following antipsychotic treatment. Likewise, while some aspects are considered more prominent in TAP (i.e., direct toxic effects), no particular mechanism is known that is associated exclusively with one type of antipsychotic. However, several hypotheses have been proposed to explain TD independent of the antipsychotic class. In the next paragraph, we briefly describe the most common and widely studied mechanisms without providing a conclusive list of all hypotheses (i.e., other mechanisms have been associated with TD, such as altered synaptic plasticity, neurotoxicity, and defective neuroadaptive signaling, that are not included here).

Clinical data suggest that TD is related to DA dysregulation. In particular, TD can be caused by long-term treatment with DA-blocking agents (i.e., mostly, but not exclusively, antipsychotics). Therefore, it has been proposed that changes caused by long-term blockade of DA receptors might lead to TD. This theory suggests that TD is caused by D_2 receptor upregulation, with subsequent DA hypersensitivity [55, 56]. This has been confirmed in rodent models, which have mostly shown reversible D_2 receptor upregulation following exposure of DA receptor blockers (for review, see Cloud et al. [57] and Casey [58]) to be associated with behavioral changes (i.e., orofacial dyskinesia) [59]. In contrast, results from human imaging and immunohistochemistry studies (i.e., post mortem studies) have been conflicting [60, 61]. In fact, evidence is growing that associating TD only to DA antagonism falls considerably short. Indeed, TD may be associated with other receptors (e.g., serotonergic receptors). Serotonin has an important influence on DA release. For instance, TD following treatment with selective serotonin reuptake inhibitors (SSRIs) may be caused by the inhibition of DA neurons. It has been speculated that blocking serotonin receptors would increase the release of DA in the raphe nucleus and inhibit DA production in the basal ganglia and may cause TD. This theory has been challenged by DA-receptor occupancy measures [58]. However, more generally, we may speculate that the decreased production of serotonin could contribute to the pathogenesis of TD, albeit without knowing the specific mechanism. In addition, the involvement of γ-aminobutyric acid (GABA) in TD is still debated. Evidence does indicate that an imbalance between DA and GABA could cause TD [62]. Reduced GABA levels were detected in animal models (e.g., in the substantia nigra and external pallidum in monkeys) [63] post mortem and in the spinal fluid of humans with TD [64]; however, again, results were conflicting (e.g., decreased GABA levels in the spinal fluid could not be confirmed) [65]. In addition, a very interesting report on a study in 23 Cebus paella (capuchin) monkeys recently suggested that defective adaption in aminergic and glutamatergic neurotransmission in the striatum was associated with TD [66]. Furthermore, morphological changes focusing on cholinergic interneurons following antipsychotic exposure were detected, for instance, in rats [67], yet the relevance of these findings for TD is unclear [68]. Likewise, neuropathological examination of baboons with TD detected a reduced density of cholinergic neurons in the nucleus basalis Meynert but not the striatal cholinergic interneurons (for review, see Blanchet et al. [68]). Thus, although multiple hypotheses involving various neurotransmitters have been formulated, results are inconclusive, and the impact of these transmitters on the pathophysiology of TD remains elusive.

Literature on the genetic origins of TD is more consistent, demonstrating increased genetic vulnerability for TD in some families (i.e., a concordance for TD among first-degree relatives) [69–72]. Moreover, multiple associations of candidate gene polymorphisms and TD have been identified [73]. In the future, this aspect may be of clinical relevance if we can identify genetic biomarkers that may predict individual susceptibility to antipsychotic-induced side effects.

Another putative cause of TD is oxidative stress [74]. The oxidative stress hypothesis is based on the fact that increasing DA synthesis and metabolism results in an increased production of free radicals. In addition, DA itself causes lipid peroxidation. Changes in antioxidant enzymes can then lead to cell death. Interestingly, brain areas of the

so-called motor loop are highly relevant for motor control in schizophrenia [75–80] and, at the same time, are highly innervated with DA neurons (i.e., the basal ganglia or the substantia nigra). They may, therefore, be particularly vulnerable to oxidative stress and consequently TD [57]. Indeed, alterations of the motor system have already been found in first-episode medication-naïve subjects [81]. Likewise, alterations in motor white matter pathways have been reported in subjects with chronic schizophrenia and TD [82]. In summary, the causes of TD may be manifold, and definite conclusions remain to be drawn, with more data to come. Finally, we must recognize that various substances other than antipsychotics are associated with TD (i.e., antidepressants, anticholinergic agents, antihistamines, and antiemetics; for review, see Cornett et al. [11]).

4 Management

No single optimal treatment strategy for TD exists. Clinicians must thus focus on restricted use of the noxious agents and early detection. This section summarizes the best available management options, noting that evidence is limited. One critical aspect for the management of TD is its detection and classification. TD is not easy to detect in the clinical interview, putative causes of TD are not always evaluated, and patients sometimes lack awareness of TD symptoms [83]. Dyskinesia has been described in drug-naïve patients, and early (acute) dyskinesia has been observed after administration of antipsychotics and following long-term treatment with antipsychotics. In addition, TD may wax and wane. Some reports suggest that patients in whom drug-induced motor symptoms (extrapyramidal symptoms) appear early in the disease are more likely to develop TD. Thus, evaluation of TD before the administration of an antipsychotic and at various time points during treatment is warranted. It is evident that causes of TD (i.e., type of medication and neurological or other somatic disorder) are relevant for the management of and treatment decisions for TD and must be carefully evaluated [84]. However, if dyskinesia is diagnosed in a patient using a DA-blocking agent (often an antipsychotic) without a neurological disorder, other aspects play a major role in the management and treatment of TD [84]. Rating scales aid the reliable detection of TD, and instrumental assessments have proven useful in identifying TD and other motor symptoms [9, 85]. For instance, evidence indicates that early extrapyramidal symptoms may predict later TD [54]. In addition, ratings of symptom severity and of disability due to TD are essential for treatment decision making. In fact, after diagnosing TD, the main question is whether the patient experiences the TD, either physically (e.g., speaking or eating is disturbed) or psychologically (e.g., TD often induces feelings of shame). While the severity of TD is related to patient outcome (i.e., global functioning) [43, 86], some patients suffer when affected by a relatively mild form of TD, whereas others do not notice even severe TD. Moreover, TD localization (focal vs. generalized) affects the treatment strategy. Finally, the course of TD must be considered, for instance, in some cases, dyskinesia extends from the orofacial region to the upper or lower limbs during the course of the disorder, indicating a need for treatment strategies to be adapted [87].

Prevention is the best strategy for the management of TD (Fig. 1), including limiting the exposure to and dosages of antipsychotics whenever possible [88]. The use of antipsychotics has increased over the years, for two reasons: first, indications for some antipsychotics have broadened to include bipolar disorders, and second, a substantial group uses antipsychotics for non-psychotic conditions such as autism, behavioral disorders, and sleep problems. Alternative pharmacological or non-pharmacological interventions are often available for non-psychotic disorders [16]. Some clinicians use antipsychotics to treat TD. Critically, withdrawal of antipsychotics may acutely worsen TD symptoms. In fact, the beneficial (probably suppressive) effects of TAPs on TD can be impressive. In contrast, some evidence indicates that this effect diminishes over time [89, 90], requiring further dosage increases. On the other hand, an 18-year prospective cohort study indicated that increasing the dosage, adding an AAP, or switching to a TAP reduced TD, an effect that did not diminish over time. However, this strategy is not

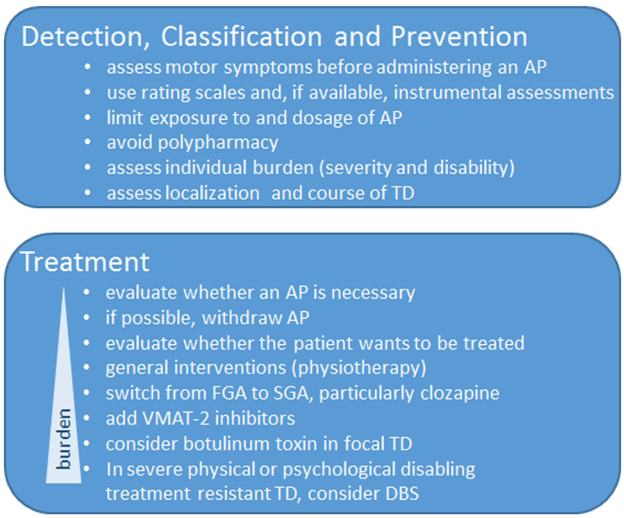

Fig. 1 Management of tardive dyskinesia associated with atypical antipsychotics. *AP* antipsychotic, *DBS* deep-brain stimulation, *FGA* first-generation antipsychotic, *SGA* second-generation antipsychotic, *TD* tardive dyskinesia, *VMAT-2* vesicular monoamine transporter-2

recommended as it may increase or initiate other side effects, such as parkinsonism, cognitive impairment, weight gain, and diabetes mellitus [91].

Moreover, it has been suggested that AAPs (quetiapine, clozapine, risperidone, aripiprazole, and olanzapine) are not only safer in terms of TD incidence but can also be a treatment for TD [92–94]. In particular, a switch to clozapine in patients with moderate to severe TD is often very effective [95–97]. Whether other AAPs improve TD in the long term is still unclear [57]. It is most likely that cumulative exposure to antipsychotics, including AAPs, is critically linked to the occurrence and—most importantly—the irreversibility of TD. Thus, to prevent TD, it is suggested that treatment with antipsychotics be limited if possible.

However, evidence that restrained exposure to antipsychotics is beneficial for TD is limited [98]. Rates of TD remission are unclear and variable, with some risk factors, such as age and duration of antipsychotic exposure identified (and replicated) [40]. Only two RCTs in first-generation antipsychotics investigated the effect of dose reduction on TD [99, 100]. In fact, a significant reduction in TD symptoms, together with greater morbidity and higher relapse rates, were detected in patients in whom antipsychotic dosage was reduced [99]. In line with this, some observational studies have reported that a reduction in antipsychotic dose had a positive effect on TD: TD symptoms improved for patients whose antipsychotic medication was reduced or discontinued compared with those whose dosage was kept stable or increased [101–103]. In contrast, Koshino et al. [86] found dose reduction had no effect on TD. In fact, the long-term outcome (11–12 years) of TD in their patients was not associated with discontinuation, increase, or decrease of antipsychotic dosage. Adding an AAP to an existing TAP treatment was associated with a reduction in TD severity [91]. Furthermore, Yagi and Itoh [104] found that dose reduction improved TD but also hypothesized that the long-term outcome of TD is determined by the patient's age at onset rather than the course of treatment after the occurrence of TD. To conclude, some evidence, from both RCTs and observational studies, indicates that a reduction in the dose of antipsychotics has a positive effect on the long-term outcomes for TD; however, results are inconsistent and are from very small samples.

Likewise, evidence as to whether switching from one antipsychotic drug to another ameliorates TD is only limited. Some trials demonstrated an improvement in TD after switching to a different antipsychotic versus antipsychotic withdrawal (i.e., risperidone or haloperidol vs. placebo). The results indicated that risperidone may have beneficial effects on pre-existing TD [92, 105, 106]. In addition, a few studies have explored the effect of switching antipsychotic medication, i.e., switching to an AAP (amisulpride, clozapine, olanzapine, risperidone, quetiapine, ziprasidone) compared with switching to either a TAP or another AAP [93, 106–109]. These studies indicated small benefits when switching from haloperidol to quetiapine (after 6 months), particularly regarding the need for antiparkinson drugs [108, 110], but no difference between patients receiving risperidone or haloperidol. In addition, the incidence of extrapyramidal symptoms at 6 months (as measured by the Extrapyramidal Symptom Rating Scale) seemed to be lower in patients receiving olanzapine than in those receiving risperidone [93], whereas no differences in TD were detected between those receiving quetiapine versus risperidone or ziprasidone [109, 111]. As such, treatment with olanzapine might be more acceptable and associated with fewer dropouts (people leaving the study early).

Aripiprazole, another AAP, is thought to have a low risk of some extrapyramidal symptoms such as parkinsonism but may be frequently associated with akathisia [112]. It has also been reported that switching from other medications to aripiprazole can improve TD [113]; however, other reports have indicated that aripiprazole may also induce TD [114]. Thus, it is unclear whether aripiprazole is effective in the treatment of TD, and if so, whether it is more effective than other AAPs [94].

Finally, clozapine is the prototypical antipsychotic with a lower frequency of acute drug-induced movement disorders. While the frequency is assumed to be the lowest among AAPs [36], clozapine can also clearly cause TD [30] (for a review, see Hazari et al. [38]), even in patients receiving clozapine as a first-line antipsychotic drug [20]. However, as clozapine is not approved as a first-line treatment, most patients with clozapine have already been exposed to another antipsychotic, which hampers the detection of a clear association with TD among these patients. In summary, the limited available data provide no clear evidence for a benefit from switching antipsychotics, particularly within classes, with the possible exception of clozapine, which is thought to have the lowest frequency of TP.

All in all, the available data suggest that antipsychotics should not be used systematically to treat TD [16]. In patients in whom antipsychotics cannot be withdrawn, switching from a TAP to an AAP (or at least to lower-potency drugs) is recommended, albeit evidence to support the advantage of one particular AAP is limited, except for clozapine. From a clinical perspective, and keeping in mind the profile of DA-receptor occupancy and dissociation, switching the treatment to quetiapine, if clozapine is not tolerated, may be helpful in patients with TD. Finally, future studies evaluating the general benefits for patient outcomes of long-term antipsychotic treatment are

warranted and are clearly necessary to develop truly individualized antipsychotic treatment recommendations [115].

Apart from antipsychotic therapy (specific antipsychotic drugs, dose reductions, or intermittent therapy) [88], various other pharmacological interventions have been studied as primary or add-on (with continued antipsychotic therapy) treatment, and the results have been systematically reviewed [84]. Possible substances include GABA agonists [116], benzodiazepines [117], anticholinergics, cholinergics, calcium channel blockers [118], and noradrenergics [119]. Supplements such as fatty acids or vitamins [120, 121] have also been investigated. However, we must conclude, from the available data, that the effect of cholinergics, GABA agonists, and calcium channel blockers remains unclear.

Trials of benzodiazepines have compared diazepam or clonazepam with placebo, treatment as usual, or phenobarbital as active placebo [122–124], with all arms continuing antipsychotics, and yielded conflicting results. One trial suggested diazepam was not effective in managing TD [122], and others reported that clonazepam might be beneficial, or at least more beneficial than phenobarbital [123, 125]. Alabed et al. [116] conducted a systematic meta-analysis in 2011 to review the effect on TD of benzodiazepines and non-benzodiazepine GABA agonists (i.e., valproate or baclofen); they concluded that any possible benefits are likely to be outweighed by the associated adverse effects. To our knowledge, no RCT has been performed since then, and no ongoing clinical trial is currently registered with clinicaltrials.gov.

One double-blind, placebo-controlled study observed ten patients with chronic schizophrenia and pronounced TD symptoms who were receiving long-term treatment with antipsychotics and anticholinergics and were withdrawn from anticholinergic medication (biperiden). The severity of TD decreased significantly in nine patients within 2 weeks (AIMS); this improvement, most pronounced in the oral region, persisted during a 6-week placebo period. Hence, discontinuation of anticholinergic medication, if administered, is a possible therapeutic approach in patients with TD. However, at the same time, parkinsonian symptoms slightly increased, and some patients may find this more troublesome than TD [126].

Furthermore, it has been proposed that high doses of free radical scavengers (i.e. vitamin E) can reduce the severity of TD, but results are conflicting and most likely show no significant effect [121]. This was confirmed by Bergman et al. [98] in their recent overview of results of RCTs of vitamin E. They used relatively strict inclusion and exclusion criteria to identify 13 trials on vitamin E and antipsychotic continuation compared with placebo and antipsychotic continuation. Results remained inconclusive, with most—but not all—reports showing no significant effect from vitamin E. However, the authors also rated the quality of the evidence in the included trials as low to very low [98].

In addition, one 12-week double-blind RCT tested the effect of levetiracetam on TD and found a moderate reduction of TD (mechanism unclear, with some suspected effects on GABA as agonist) [127]. Similarly, three trials recently examined the antioxidant extract of Gingko biloba (EGb-761) as a treatment option for TD; the authors observed a beneficial effect. Larger placebo-controlled RCTs are needed to evaluate the impact of these effects. For further information on additional supplements (e.g., Yi-gan san), see Caroff et al. [84].

VMAT-2 inhibitors (i.e., tetrabenazine, valbenazine, deutetrabenazine) are probably the most interesting "new" approach to the treatment of TD. Tetrabenazine has been shown to be effective in both single cases and small samples [128–130]. One early RCT compared haloperidol and tetrabenazine for 18 weeks in patients with TD. The frequency of oral dyskinesia declined, with no differences between the two substances or groups [131]. A recent meta-analysis [84] thoroughly reviewed the most recent short-term double-blind RCTs (see Table 1). Based on these data, the FDA approved valbenazine as the first drug and deutetrabenazine as the second drug for the treatment of TD. VMAT-2 inhibitors, both as monotherapy and as adjuvants to antipsychotic drugs, have been investigated in short-term trials, but longitudinal studies (>48 weeks) are lacking. Therefore, Caroff et al. [84] found clear evidence for the efficacy of valbenazine and deutetrabenazine in treating TD while also acknowledging the need for long-term observations. They particularly highlighted the theoretical risk that VMAT-2 inhibitors may worsen TD or cause new cases to develop [84]. Thus, VMAT 2- inhibitors seem to be effective for the treatment of TD, pending long-term observations to enable conclusions about management strategies for TD, particularly keeping in mind the lack of information about safety aspects such as serious dose-dependent side effects.

Botulinum toxin injections are a promising treatment option for localized orofacial TD. Case studies and some small open-label investigations have indicated that repeated botulinum toxin injections, for instance into the genioglossus muscles, can be effective (moderate or marked improvement) and relatively safe [137–141]. Interestingly, spreading of the response to additional muscle groups has been reported. The average duration of effect (about 12 weeks) is comparable with that in other patient groups receiving botulinum toxin injections (i.e., patients with dystonia due to other causes) [140]. The most significant risk of the therapy is severe dysphagia. Considering the risks, the treatment is relatively safe with a low level of

Table 1 Recent clinical trials of vesicular monoamine transporter-2 inhibitors

Study	Year	Study design	Substance
O'Brien et al. [132] KINECT 2	2015	6-week PC DB RCT	Valbenazine
Hauser et al. [133] KINECT 3	2017	6-week PC DB RCT	Valbenazine
Josiassen et al. [134] LTE population (KINECT, KINECT 3, KINECT 4)	2017	Pooled LTE (48 weeks of treatment), DB, randomized, PC trials	Valbenazine
Fernandez et al. [135] ARM-TD	2017	12-week PC DB RCT	Deutetrabenazine
Anderson et al. [136] ARM-TD	2017	12-week PC DB RCT	Deutetrabenazine

All studies used the AIMS as a TD rating scale

AIMS abnormal involuntary movement scale, *DB* double-blind, *LTE* long-term exposure, *PC* placebo-controlled, *RCT* randomized controlled trial, *TD* tardive dyskinesia

adverse effects [139] and can be recommended in specific cases.

Moreover, uni- or bilateral pallidal [globus pallidus interna (GPi)] deep brain stimulation (DBS) has been investigated in case reports and small patient cohorts with TD [142–145]. Reports on thalamic or subthalamic stimulation are also available [144, 146]. The available data indicate that pallidal stimulation has heterogeneous effects, with most cases experiencing at least moderate improvement in TD [147], but evidence is limited. As in other DBS indications, the onset of benefit can be immediate or take months. Initial data indicate long-term effects last up to several years [148]. Taken together, DBS should be considered in severe treatment-resistant TD. DBS seems to be a promising and effective treatment in these patients and can provide sustained alleviation of facial, axial, or limb symptoms [149]. However, effective stimulation methods and parameters are unclear, and randomization, sham control groups, blinded assessment, and longer-term follow-up are necessary in these groups.

Although various treatments for TD have been studied (for Cochrane reviews on the pharmacological treatment of TD see Table S1 in the Electronic Supplementary Material), no clear treatment algorithm can be constructed. We think, based on the limited evidence and our own clinical experience, the interventions holding the most promise include switching to clozapine, adding VMAT-2 inhibitors, or administering botulinum toxin injections in focal TD (Fig. 1).

5 Conclusion

TD continues to be a problem in the era of AAP. It is a frequent disorder that can occur in early stages of the disorder and intensify with increasing age and duration of illness, even in patients treated with AAPs. Unfortunately, TD is irreversible in many patients. Detection of TD relies on the use of clinical rating scales or instrumental assessments. The pathophysiology underlying the disorder remains unclear and the management of TD complex. Promising treatment options have been developed, but available data are inconclusive and sometimes low quality. Importantly, to evaluate the clinical relevance of TD, both severity and the functional and social consequences of the disorder must be considered for each patient. Based on the available data and our own experience, we suggest that switching to clozapine, adding VMAT-2 inhibitors, or administering botulinum toxin injections in focal TD are currently the most promising interventions for TD when intervention is necessary. However, data are limited and—thus far—the best management strategy remains prevention.

Funding No sources of funding were used to prepare this manuscript.

Compliance with Ethical Standards

Conflict of Interest In the last 10 years, Sebastian Walther has received honoraria for serving as a speaker in educational programs from Eli Lilly, Janssen, Lundbeck, and Otsuka. He was an advisory board member for Lundbeck and Otsuka from 2015 to 2016. Katharina Stegmayer and Peter van Harten have no conflicts of interest.

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