EXPERT REVIEWS

Tardive dyskinesia and withdrawal emergent syndrome in children

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Tardive dyskinesia (TD) is a well-recognized and sometimes permanent adverse effect of treatment with dopamine receptor-blocking drugs (DRBDs), also referred to as neuroleptics. This iatrogenic disorder has been well characterized in adults, but not extensively studied in children. Withdrawal emergent syndrome (WES) is another pediatric movement disorder related to the use of DRBDs. TD and WES are among the most feared adverse effects of DRBD treatment, and have important medical and legal implications. We review published studies of children under the age of 18 years who were exposed to DRBD to determine the clinical spectrum and estimate the possible prevalence of TD and WES. We particularly wish to draw attention to the phenomenology, clinical course and treatment of these childhood-onset disorders. Although avoiding DRBDs is the best strategy for minimizing the risk of TD and WES, physicians who evaluate children exposed to DRBDs must be vigilant and recognize the early symptoms and signs of these syndromes to provide appropriate clinical management.

Keywords: antiemetic • antipsychotic • children • dopamine • metoclopramide • neuroleptic • pediatric • tardive • tardive dyskinesia • tetrabenazine • withdrawal emergent syndrome

Tardive dyskinesia (TD) is a hyperkinetic movement disorder temporarily and causally related to exposure to dopamine receptor-blocking drugs (DRBDs), also referred to as neuroleptics. TD is a well-recognized and sometimes permanent iatrogenic disorder in adults, but may also occur in children [1,2]. Withdrawal emergent syndrome (WES) is a variant of drug-induced movement disorders, characterized by generalized choreic movements in children in whom DRBDs are abruptly withdrawn and whose symptoms tend to resolve spontaneously after several days or weeks [3,4]. Although published reports on TD mainly focus on adults who have been exposed to DRBDs used as antipsychotics, these dopamine-blocking medications are also used to treat a wide array of pediatric neurological (e.g., tics) and medical (chiefly gastrointestinal) conditions [5]. It is imperative for physicians to recognize that children treated with DRBDs are at risk for the development of drug-induced movement disorders, such as TD and WES. We review published studies on TD and WES in children, focusing on understanding various risk factors, the natural course of disease, treatment modalities and clinical outcomes of children affected with these syndromes.

Methods

We identified studies on TD and WES in children that were listed in PubMed between 1953 and 2009. All tardive syndromes (tardive stereotypy, chorea, dystonia, akathisia, tics, myoclonus and tremor) were included [1]. We also incorporated studies that described WES. Keywords systematically searched in PubMed included: tardive, tardive dyskinesia, tardive stereotypy, tardive chorea, tardive dystonia, tardive akathisia, tardive tic, tardive myoclonus, tardive tremor, withdrawal emergent syndrome, hyperkinetic movement disorders, neuroleptic, antipsychotic, dopamine receptor blocker, metoclopramide, pediatric and children. We conducted additional searches of pertinent articles cited in our reference sources. We selected all articles on TD and WES that provided data on patients up to 18 years old who fulfilled the following inclusion criteria: exhibited a movement disorder; documented exposure to one or more DRBD for at least 3 months before the onset of TD or WES symptoms (shorter exposure time to DRBD was accepted if this seemed to be related to the development of TD); and, in the case of TD, the hyperkinetic movement disorder persisted for at least 1 month after stopping the offending

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DRBD [1,6]. In total, 17 articles met our TD inclusion criteria; of these, seven were prospective studies (n = 569 patients) [7–13], one was a retrospective study (n = 125 patients) [14] and nine were case reports (n = eight patients) [15–23]. WES cases were reported in three of the series that included TD patients, in one additional series that focused on WES and in two case reports [7,9–11,21]. Relevant data concerning patient demographics, medication history, topographic findings, treatment of TD or WES and clinical outcome were abstracted from every study. One study included 38 patients up to 21 years of age, but data were included for only a subsample of 12 patients under 13 years of age [9]. Two studies focused on the use of atypical antipsychotics in children [12–13]. We identified six additional articles not incorporated in our analysis because they represented subsamples of the 118 children enrolled in the original long-term prospective study by Campbell and colleagues, published in 1997 [10,24–29]. Nine case reports [30–38], five prospective [39–43] and three retrospective studies [44–46] were also excluded from our analysis because they failed to meet one or more of our inclusion criteria, usually owing to including patients older than 18 years in their analysis or because of incomplete information.

Results

The 17 reviewed studies of TD and WES in children provide data on a total of 702 patients aged 1–18 years (Tables 1 & 2) [7–23]. Children were treated with DRBDs for various psychiatric conditions (n = 463; 65.9%), autism (n = 118; 16.8%), mental retardation (n = 116; 16.5%), Tourette syndrome (n = 5; 0.7%) and gastroesophageal reflux disease (n = 2; 0.3%). Of the studied children, 361 (51.4%) were in-patients, 110 (15.7%) were out-patients, 233 were combined in-patients and out-patients (33.2%) and an additional 118 (16.8%) were in-patients who were then followed as out-patients over the course of 15 years [10].

Tardive dyskinesia was reported in 69 of the 702 (9.8%) patients aged 1–18 years who were exposed to DRBDs. In total, 27 of the 69 (39.1%) were male, 21 were female (30.4%) and gender was not specified for the other 21 (30.4%) patients. The youngest patient with documented TD was a 12-month-old girl who developed orofaciolingual stereotypy at 2 months of age after 2 weeks of treatment with metoclopramide for gastroesophageal reflux disease; the stereotypy was documented by sequential videos and persisted for at least 9 months after the DRBD was discontinued [23]. The cause of TD in the 69 affected patients was attributed to: haloperidol (n = 12; 17.4%), risperidone (n = 11; 15.9%), thioridazine (n = 3; 4.3%), metoclopramide (n = 2; 2.9%), prochlorperazine (n = 1; 1.4%), perphenazine (n = 1; 1.4%) or fluphenazine (n = 1; 1.4%); the causative agent was not specified in 39 patients (67.2%), eight of whom had been exposed to more than one DRBD. In total, ten of the 69 TD patients (14.5%) were exposed to a DRBD for a median of 2.7 years, nine (13.0%) for a mean of 1.8 years and 11 (15.9%) for 3 years; the duration of exposure to DRBD was not reported for 39 patients (67.2%). The phenomenology of TD was poorly described but when it was characterized, it consisted chiefly of orofacial stereotypies with or without dystonic or choreic movements of the trunk and limbs. In three of the TD patients, symptoms were noted after withdrawal of the offending DRBD; the rest of the TD cases occurred while patients were still taking the DRBD [15,16,19]. The latter cases most likely represented TD and not WES, since the movements were chiefly stereotypic rather than choreic, as typically observed in WES; they involved the facial region in contrast to WES, in which the distribution of the chorea is more generalized, and lasted at least 3 months; whereas, WES movements tend to resolve spontaneously after several days or weeks. Treatment was not specified for the majority of TD patients (n = 44; 63.8%); in patients with available treatment data, this consisted of discontinuation of the offending DRBD in 19 children (27.5%) and return to treatment with the offending drug in six (8.7%). A child whose symptoms persisted beyond 5 months after discontinuation of the causative DRBD was treated successfully with deanol [17]. A total of 25 of the 69 (36.2%) affected patients had resolution or improvement of TD (15 within 1 year, but time to resolution of symptoms was not specified for the other three patients); 11 children (15.9%) had no change in symptoms, and four (5.8%) were worse than at their last evaluation by the time of their report; no clinical outcome information was provided for 29 patients (42.0%). A child whose TD resolved after 1.5 months of discontinuation of haloperidol was restarted on the same DRBD and again developed TD, requiring repeat discontinuation of haloperidol with eventual TD resolution after 1.2 months; unfortunately this patient had to be started on haloperidol a third time and again developed TD, which disappeared after decreasing the total daily dose of this medication by half [19].

Withdrawal emergent syndrome was reported in 64 of the 702 (9.1%) compiled patients, but this could be an underestimate as some patients may not have been screened specifically for WES. Haloperidol was the causative agent in 38 out of the 64 affected patients (59.3%), fluphenazine in eight (12.5%), thiothixene in six (9.3%), thioridazine in one (1.5%) and trifluoperazine in one (1.5%); the causative DRBD was not specified for the other nine patients who developed WES (14%). All patients with WES improved: 43 (67.1%) did so without treatment and 20 (31.2%) improved after reinstitution of the DRBD, due to their psychiatric condition worsening. A 10-year-old girl with Tourette syndrome who presented with WES during a 'holiday' from pimozide had a resolution of symptoms after 2 months without treatment [21]. Another patient who developed WES was an 18-year-old girl with schizophrenia and baseline mild orofacial dyskinesias who developed dyskinesia of her hands and neck after slowly tapering off clozapine and while on treatment with perphenazine; she was then treated with risperidone and tapered from perphenazine over a 1-week period, developing incapacitating choreoathetoid and dystonic movements of neck, trunk and hips, as well as hemiballistic movements of the limbs. Although her movements only resolved after 6 months of reinstitution of clozapine, she was included as a WES patient in our analysis owing to the absence of her underlying orofacial movements worsening after withdrawal from clozapine, and because her involuntary movements were mainly choreic in nature [22].

Table 1. Case series of tardive dyskinesia and withdrawal emergent syndrome in children.

Study (year)/ type of study	Number and type of subjects	Age (years)	Sex	Diagnosis	Medication history	TD			WES			Ref
						Subjects; n (%)	Treatment	Outcome	Subjects; n (%)	Treatment	Outcome	
McAndrew *et al.* (1972)/ Retrospective	125 in-patients	4–16 (x = 13.5)	86 M 39 F	Multiple psychiatric disorders	Thioridazine Chlorpromazine Trifluoperazine	10 (8.0)	RT = 3; NS = 7	I = 3; NS = 7	NS			[14]
Polizos *et al.* (1973)/ Prospective	34 out-patients	6–12	NS	Schizophrenia	Fluphenazine Thioridazine Haloperidol Thiothixene Trifluoperazine	NS			14 (41.1)	NT = 7; RT = 7	I = 14	[7]
Paulson *et al.* (1975)/ Prospective	103 in-patients	11–16 (x = NS)	NS	Mental retardation	Chlorpromazine Thioridazine Trifluoperazine	21 (20.3)	DC = 2; RT = 2; NS = 17	I = 5; NI = 6; W = 4; LFU = 5; DTE = 1	NS			[8]
Gualtieri *et al.* (1986)/ Prospective	12 in-patients	5–13 (x = NS)	NS	Mental retardation	Thioridazine NS DRBD	2 (16.6)	DC = 2	I = 2	3 (25.0)	NT = 3	I = 3	[9]
Campbell *et al.* (1997)/ Prospective	118 in-patients, later followed as out-patients	2.3–8.2 (x = 4.9)	95 M 23 F	Autism	Haloperidol	9 (7.6)	NS = 9	I = 2; NI = 2; NS = 5	36 (30.5)	NT = 30; RT = 6	I = 35; NS = 1	[10]
Kumra *et al.* (1998)/ Prospective	34 out-patients	6–18 (x = 14.1)	19 M 15 F	Schizophrenia	Haloperidol Clozapine Olanzapine Fluphenazine Risperidone	8 (23.5)	DC = 8	I = 8	9 (26.4)	RT = 7; NT = 2	I = 9	[11]
Reyes *et al.* (2006)/ Prospective	35 out-patients	6–16 (x = 11.1)	31 M 4 F	Disruptive behavior disorder	Risperidone	0 (0)			NS			[12]
Wonodi *et al.* (2007)/ Prospective	233 in-patients and out-patients (118 exposed to atypical or typical antipsychotics for more than 6 months; 80 antipsychotic-naive; 35 healthy controls)	5–18 (x = 11.3)	165 M 68 F	Multiple psychiatric disorders	Various atypical antipsychotics	11 out of 118 antipsychotic-treated (9%), 0 out of 80 antipsychotic-naive (0%), 0 out of 35 healthy controls (0%)			NS			[13]

DC: Discontinuation; DRBD: Dopamine receptor-blocking drug; DTE: Difficult to examine; F: Female; I: Improvement; LFU: Lost to follow-up; M: Male; NI: No improvement; NS: Not specified; NT: No treatment; RT: Reinstitution; TD: Tardive dyskinesia; W: Worsening; WES: Withdrawal emergent syndrome; x: Mean.

Table 2. Case reports of tardive dyskinesia and withdrawal emergent syndrome in children.

	Number and type of subjects	Age (years)	Sex	Diagnosis	Medication history	TD		WES		Ref.
						Treatment	Outcome	Treatment	Outcome	
Browning and Ferry (1976)	One out-patient	10	M	Mental retardation	Prochlorperazine	DC	NI			[15]
Caine *et al.* (1978)	One in-patient	15	M	Tourette syndrome	Haloperidol Trihexyphenidyl	RT	I			[16]
McLean and Casey (1978)	One in-patient	12	M	Schizophrenia	Haloperidol Trihexyphenidyl Thioridazine	DC, deanol	I			[17]
Mizrahi *et al.* (1980)	One out-patient	7	M	Tourette syndrome	Haloperidol	DC	I			[18]
Caine and Polinsky (1981)	Two out-patients	8	M	Tourette syndrome	Haloperidol	DC	I			[19]
		16	M	Tourette syndrome	Haloperidol	DC	I			
Putnam *et al.* (1992)	One out-patient	8	M	Gastric reflux and erosive esophagitis	Metoclopramide	DC	NI			[20]
Kompoliti and Goetz (1998)	One out-patient	10	F	Tourette syndrome	Pimozide			NT	I	[21]
Ahmed *et al.* (1998)	One in-patient	18	F	Schizophrenia and mild orofacial dyskinesias	Clozapine Perphenazine Risperidone			Benztropine Lorazepam Baclofen Trihexyphenidyl	I	[22]
Mejia and Jankovic (2005)	One out-patient	1	F	Gastroesophageal reflux	Metoclopramide	DC	NI			[23]

DC: Discontinuation; F: Female; I: Improvement; M: Male; NI: No improvement; RT: Reinstitution; TD: Tardive dyskinesia; WES: Withdrawal emergent syndrome.

Discussion

In the studies of children exposed to DRBDs that we reviewed, 69 of the 702 (9.8%) patients were reported to have TD, less than half of the estimated 23.4% prevalence of TD in the general adult population [1]. It is challenging to estimate the possible prevalence of TD in children, as the reported studies often had considerable amounts of missing data. Furthermore, different diagnostic criteria for TD, varying patient study populations, methodological differences for patient ascertainment and the wide range of medications used contribute to the marked variability in reported estimates of TD incidence and prevalence. These epidemiologic challenges are illustrated by the wide variability in study results, with reported TD prevalence in children ranging from 8 to 20.4% [8,14]. Campbell and colleagues' methodologically rigorous prospective, and initially double-blinded transitioning to open-label, 15-year-long study estimated that 7.6% of patients exposed to DRBDs develop TD, although their study population was limited to autistic children [10]. The literature on adult series also provides a wide range of estimates of the prevalence of TD, varying from 13.3 to 36.1% of DRBD-treated patients [47,48]. It is possible that the reported figures may be an overestimate of the true prevalence of TD, as it is difficult to ascertain if all the patients reported in the literature had TD or if some of the observed movements were actually stereotypies associated with subject's baseline neurologic disease [49]. On the other hand, the reported figures could be an underestimate as drug-induced movement disorders are often not recognized by the treating physicians or are wrongly attributed to the underlying neurological or psychiatric disorder. For example, stereotypies and akathisia are often thought to be due to underlying autism, or purely to anxiety or 'nervousness'.

Tardive dyskinesia has been considered an age-related disorder, with elderly women having the highest risk [1,47,50]. In the prospective study of 38 mentally retarded patients aged 5–47 years (mean 19.4 years) who were withdrawn systematically from DRBD, age seemed to be associated with the development of moderate-to-severe TD. Two patients in the 5–13-year-old group developed TD with eventual resolution, while 11 patients in the 13–47-year-old group presented TD (five of whom had persistent symptoms) [34]. The

single variable that most highly correlated with the development of moderate or severe TD was total lifetime exposure to DRBD [9].

Our analysis of published cases does not provide sufficient evidence for gender as a TD risk factor, as a large percentage of gender data is missing. Campbell and colleagues' report that females seemed more likely to develop TD than males in their long-term prospective study of autistic children exposed to haloperidol did not reach statistical significance, but suggested a trend (17.4% females compared with 5.3% males developed TD) [10]. Conversely, the study involving 34 children with schizophrenia exposed to DRBDs who were followed for up to 4 years, did not find a statistically significant gender difference in patients who developed TD or WES versus those who did not [11].

It is important to note that WES and TD may resemble other movement disorders and should be differentiated from them not just by history of neuroleptic exposure, but also by recognizing its characteristic phenomenology and after excluding other possible causes. WES, for example, may mimic Sydenham's chorea, a late manifestation of rheumatic fever that occurs in 26% of patients 1–6 months after acute group A hemolytic streptococcal pharyngitis [51]. Both WES and Sydenham's chorea lead to movements that are brief and flow randomly from one body part to another. Sydenham's chorea may also be accompanied by tics, dysarthria, motor impersistence, gait disturbances, oculomotor abnormalities, hyperactivity, attention deficit, obsessions, compulsions and depression. Although both conditions tend to resolve spontaneously, WES usually disappears within days or weeks, while Sydenham's chorea may last more than 9 months [3,4,51].

Tardive dyskinesia may also be difficult to differentiate from stereotypies [52–54]. TD tends to involve more body areas and have greater severity than the stereotypies commonly observed in autistic patients [28]. The movements exhibited in TD may also mimic stereotypies that occur in otherwise normal children [49]. Stereotypies may be characterized as flapping (48%), shaking (28%), clenching–stiffening–posturing (38%) or ritualistic (13%) movements that usually last a few seconds, occurring daily but not during sleep. These TD-mimicking movements usually occur in children before the age of 3 years, and may be related to excitement, boredom, focusing and anxiety or stress [55].

Tardive dyskinesia and WES have been traditionally attributed to typical (first-generation) antipsychotics, yet other DRBDs and atypical (second- and third-generation) neuroleptics are emerging as an important cause of TD. Joseph Jankovic encountered a 10-year-old boy with Tourette syndrome who developed choreic tongue and arm movements 3 days after suddenly stopping aripiprazole, which resolved when aripiprazole was reintroduced and did not recur when the drug was subsequently gradually discontinued [56]. It is also important to emphasize that although most drugs with the potential to cause TD and WES belong to the antipsychotic family of drugs (phenothiazines, thioxanthenes and butyrophenones, among others), other medications used in the treatment of children for nonpsychiatric-related problems, such as metoclopramide (substituted benzamide), are also DRBDs and have the ability to cause TD. The epidemiology of metoclopramide-induced movement disorders has not been well addressed and many cases remain unreported, but in a movement disorders clinic, metoclopramide is among the most frequent causes of TD [57,58]. A review of 131 patients with drug-induced movement disorders found this DRBD to be the TD causative agent for 12% (n = 16) of patients, all of whom had been exposed to metoclopramide doses between 20 and 40 mg per day [59]. Despite conflicting data in the literature, we believe that metoclopramide is an important cause of TD in children that seems to be under-recognized and under-reported, with only two children with metoclopramide-induced TD reported in the literature [20,23]. Prospective and retrospective cohort studies are needed to determine the true prevalence of metoclopramide-induced TD in children.

Expert commentary

Tardive dyskinesia and WES are feared and potentially avoidable morbidities of DRBD treatment in children that may even increase mortality [60]. Avoiding or reducing the use of DRBD is the first step in preventing the development of TD. If a patient develops TD while still taking a DRBD, the most important management strategy is to discontinue the medication by slowly tapering the offending drug whenever possible [1,6]. Slow tapering of DRBDs will also reduce the risk of WES, which, despite being self-limited, causes great concern to patients and their families [7]. Fortunately, the majority of children affected by WES and TD do not require treatment because of the excellent prognosis for spontaneous remission of these syndromes. In the reported cases, 19 of the 69 TD patients (27.5%) improved by just discontinuing the causative agent, and all WES patients improved, usually without requiring treatment.

Although second- and third-generation neuroleptics have been promoted as having a lower risk of TD, perhaps by binding less strongly to dopamine receptors than typical neuroleptics, these drugs (including aripiprazole, olanzepine, risperidone, quetiapine, tiapride and sulpiride) have been reported to cause TD, at least in adults [12,13,56,61–65]. In long-term studies, the incidence of TD due to first-generation antipsychotics is thought to be 5% per year in all adults and approximately 25–30% in more elderly patients, while no children exposed to second-generation antipsychotics have yet been reported to develop TD [65]. However, with long-term use it is likely that new cases of TD or WES will be encountered in children as a result of exposure to atypical neuroleptics. Tardive syndromes have not been reported in patients treated with dopamine-depleting drugs, such as tetrabenazine, a synthetic benzoquinolizine that acts as a monoamine-depleting drug by inhibiting the central vesicular monoamine transporter type 2 [66,67]. Although approved by the US FDA in 2008 for the treatment of adults with chorea associated with Huntington disease, tetrabenazine is considered the off-label treatment of choice in patients with troublesome TD, including children [68–71]. Similar to DRBDs, tetrabenazine may cause dose-related drowsiness, depression, restlessness and parkinsonism, but in contrast to DRBD, it has not been associated with TD.

Five-year view

It will be necessary to continue supporting methodologically rigorous prospective clinical studies of children exposed to DRBDs as a way to monitor the incidence and prevalence of TD and WES. Population-wide, government-run pharmacovigilance studies should also be strictly advocated for any commercially available medication with a dopamine-blocking effect, especially if this will be used in children. Although the risk of TD and WES may be lower with 'atypical neuroleptics' than with first-generation DRBDs, we anticipate that these iatrogenic disorders will also occur with these newer and future generations of neuroleptics that act by blocking dopamine receptors. A 2009 government-mandated 'black-box' warning on the risk of TD with metoclopramide will ideally decrease the use of this medication in adults and children [72]. The FDA approval of tetrabenazine will hopefully decrease the frequency of TD in patients who are treated for chorea with this medication instead of typical neuroleptics, and will also provide an off-label treatment option for patients who develop TD (ideally leading to an extension of the FDA approval of tetrabenazine for this condition) [67]. It may be possible to consider surgical intervention with deep-brain stimulation therapy for patients with severe TD who do not improve with currently available treatments [73,74].

Exciting advances in the fields of genetics and neuroimaging will provide us with a better understanding of the pathophysiology of TD and WES. Recent scientific pursuits include a genome-wide association study of movement-related adverse antipsychotic effects [75,76]. Associations between TD and serotoninergic variants, D3 and D4 receptors, the orphan nuclear receptor NR4A1, S100B serum levels, NADPH quinine oxidoreductase 1 gene (*NQO1*), superoxide dismutase 2 genes (*SOD*, *MnSOD*), *MDR1* gene, Par-4 gene (*PAWR*), as well as polymorphisms in BDNF val-66met, GSK-3β-50T/C and gluthatione *S*-transferase have recently been described [77–89]. Furthermore, early work using dopamine transport imaging has recently provided insights into striatal dopamine transport density changes in patients with TD [90]. These and future insights into the pathophysiology of TD will hopefully help guide clinicians in their treatment of children to avoid the morbidity and potential mortality associated with DRBD.

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Key issues

- Tardive dyskinesia (TD) and withdrawal emergent syndrome (WES) are important iatrogenic disorders that affect not only adults but also children.
- Because TD and WES are neurologic movement disorders that are not often recognized in pediatric patients, they may have medical and legal implications.
- All physicians must be able to recognize the early symptoms and signs of TD and WES in patients who are exposed to dopamine receptor-blocking drugs (DRBDs) to provide appropriate clinical management.
- Avoiding DRBD treatments is the best approach to minimizing the risk of TD and WES.
- When children exposed to DRBDs develop TD, withdrawal of the offending drug should be the first management strategy. Slow dose reduction of DRBD may also prevent the occurrence of WES. If these strategies fail, various pharmacological treatments, such as tetrabenazine, should be considered.
- More research is needed to better understand the pathophysiology of TD and WES, as well as to develop new medications without dopamine receptor antagonism that are able to treat conditions in which DRBDs are currently employed.

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