Medications Associated with the Onset of Tardive Dyskinesia

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ABSTRACT

OBJECTIVE: To define the offending drugs associated with the occurrence of tardive syndromes (TS). **BACKGROUND:** Tardive dyskinesia (TD), a hyperkinetic movement disorder causally related to exposure to dopamine receptor blocking drugs (DRBD), is a well-recognized iatrogenic condition. Although the published reports on TD mainly focus on patients who have been exposed to DRBD used as anti-psychotics, these medications are also used to treat a wide array of medical, chiefly gastrointestinal, conditions. **METHODS:** A retrospective chart review was performed on subjects evaluated for TD in the Movement Disorders Clinic at Baylor College of Medicine who were enrolled in our trial of tetrabenazine (TBZ). Demographic and clinical data were ascertained. **RESULTS:** A total of 116 patients with TD currently treated with TBZ; we report data on 89 (76.7%) for whom we have complete clinical information. The patients, 74 female (83.1%), aged 62.3 ±13.9 years at their initial evaluation, had a mean age of TD onset at 58.6 ± 14.1 years. A causal DRBD was well defined in 81 (91.0%) patients. The most common drugs associated with the onset of TD were metoclopramide (N= 23, 25.8%), haloperidol (N= 9, 10.1%), and the combination of amitriptyline and perphenazine (N= 9, 10.1%). **CONCLUSION:** TD, a feared and common side effect of DRBD treatment, may be caused by multiple treatment agents other than anti-psychotic medications.

INTRODUCTION

Tardive dyskinesia (TD), a hyperkinetic movement disorder temporarily and causally related to exposure to dopamine receptor blocking drugs (DRBD), also referred to as neuroleptics, is a well-recognized iatrogenic condition particularly in adults [Stacy and Jankovic, 1991; Rodnitzky, 2005] as well as in children, including infants [Mejia and Jankovic, 2005a]. Although the literature on TD mainly focuses on patients who have been exposed to DRBD used as anti-psychotics, these medications are also used to treat a wide array of medical, chiefly gastrointestinal, conditions [Tonini, 2004; Paulson, 2005] [Table 1]. Most of the drugs that cause TD are DRBD that block dopamine D2 receptors, but other classes of drugs have the potential to cause TD [Table 2]. The reported frequency of TD in patients treated with DRBD has varied greatly, with an average at around 25% of exposed adults, and half that frequency in children [Stacy and Jankovic, 1991; Mejia and Jankovic, 2005b]. Risk factors associated with the development of TD include advanced age, female gender, and total cumulative drug exposure [Woerner et al, 1998; van Os et al, 1997; Fernandez et al, 2003; Wonodi et al, 2004].

Table 1. Conditions and procedures that may require DRBD therapy.

Gastrointestinal	Nausea, vomiting, GERD, diabetic gastroparesis; gastrointestinal imaging.
Psychiatric	Anxiety, depression, schizophrenia, bipolar disorder, alcoholism.
Neurological	Tourette syndrome, migraines, epilepsy.
Other	Menopausal symptoms, labyrinthine disorders, peripheral and cerebral vascular disorders, dermatological problems; anesthesia.

Table 2. Medications with the potential to cause TD.

Medication class	Examples
Phenothiazines	
a.Aliphatic	Chlorpromazine (e.g. Thorazine)
	Triflupromazine (e.g. Vesprin)
b.Piperidine	Thioridazine (e.g. Mellaril)
	Mesoridazine (e.g. Serentil)
c.Piperazine	Trifluoperazine (e.g. Stelazine)
	Prochlorperazine (e.g. Compazine)
	Perphenazine (e.g. Trilafon)
	Fluphenazine (e.g. Prolixin)
	Perazine
Thioxanthenes	
a.Aliphatic	Chlorprothixene (e.g. Tarctan)
b.Piperazine	Thiothixene (e.g. Navane)
Butyrophenones	Haloperidol (e.g. Haldol)
	Droperidol (e.g. Inapsine)
Diphenylbutylpiperidine	Pimozide (e.g. Orap)
Dibenzazepine	Loxapine (e.g. Loxitane)
Dibenzodiazepine	Clozapine (e.g. Clozaril)
	Quetiapine (e.g. Seroquel)
Thienobenzodiazepine	Olanzapine (e.g. Zyprexa)
Pyrimidinone	Risperidone (e.g. Risperdal)
Benzisothiazole	Ziprasidone (e.g. Geodon)
Benzisoxazole	Iloperidone (e.g. Zomaril)
Substituted benzamides	Metoclopramide (e.g. Reglan)
	Tiapride
	Sulpride
	Cleboprride
	Remoxipride
	Veraliprride
	Amisulpride
Indolones	Molindone (e.g. Moban)
Quinolinone	Aripiprazole (e.g. Abilify)
Tricyclic	Amoxapine (e.g. Asendin)
Calcium channel blockers	Flunarizine (e.g. Sibelium)
	Cinnarizine (e.g. Stugeron)
N-acetyl-4-methoxytryptamine	Melatonin

METHODS

A retrospective chart review was performed on subjects evaluated for TD in the Movement Disorders Clinic at Baylor College of Medicine who were enrolled in the compassionate protocol of TBZ under a Claimed Investigational Exemption for a New Drug (IND) awarded to one of the authors (JJ) in 1979. We included patients who: 1) exhibited a hyperkinetic movement disorder, 2) had a documented exposure to one or more DRBD for at least 3 months before the onset of symptoms (shorter exposure time to DRBD was accepted if this was clearly related to the development of TD), and 3) the hyperkinetic movement disorder persisted for at least one month after stopping the offending DRBD [Jankovic, 1995]. Demographic and clinical data were ascertained. We attempted to not only identify the causal DRBD in all TD cases, but also searched for information about dose, treatment duration, and drug free intervals, but this data was often lacking or not available.

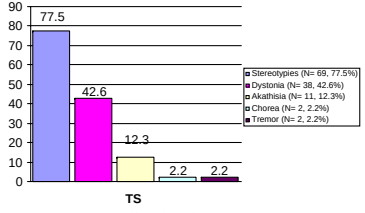
RESULTS

A total of 116 TD patients currently treated with TBZ were listed in the TBZ database. We report data on 89 (76.7%) of them, for whom we have complete clinical information. Patients, 74 female (83.1%), aged 62.3 ± 13.9 years at their initial evaluation, and had a mean age of TD onset at 58.6 ± 14.1 years. The most frequent phenomenology that patients exhibited, alone or in combination with other TS, were stereotypies (N= 69, 77.5%), dystonia (N= 38, 42.6%), and akathisia (N= 11, 12.3%) [Figure 1]. A specific causal DRBD was defined for 81 (91.0%) patients. The most common medications associated with the onset of TD were metoclopramide (N= 23, 25.8%), haloperidol (N= 9, 10.1%), the combination of amitriptyline and perphenazine (N= 9, 10.1%), and risperidone (N= 7, 7.9%) [Figure 2].

Table 3. Demographic and clinical characteristics of 89 TD patients.

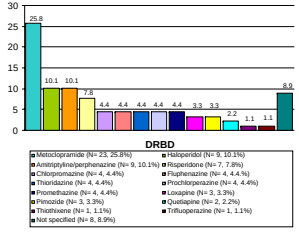
	Characteristics
Sex	74 (83.1%) female
Age	
TD onset (yrs)	58.6 ± 13.9 (21.0-93.0)
Initial dx (yrs)	62.3 ± 14.1 (24.5-94.2)
DRBD indication	
Psychiatric	52 (58.4%)
Gastrointestinal	31 (34.8%)
Other	6 (6.7%)

Figure 1. TS presented in 89 patients*.



* > 1 TS was presented by 26 (29.2%) patients.

Figure 2. Medications associated with the onset of TD in 89 patients.



CONCLUSIONS

- Although most drugs with the potential to cause TD belong to the antipsychotic family of drugs (phenothiazines, thioxanthenes, butyrophenones, etc), *other medications for non-psychiatric-related problems, such as metoclopramide (substituted benzamide), are also DRBD and have the ability to cause TD*.

- *Metoclopramide seems to be one of the most common causes of TD in adults*. A previous review of 131 patients with drug-induced movement disorders at our institution 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/day [Miller and Jankovic, 1989]. Another study of metoclopramide-treated adult patients reported that 29% (n=15) met criteria for TD, compared with 17.6% (n= 9) of metoclopramide non-users (P = 0.08) [Ganzini et al, 1993].

- Although we believe that metoclopramide is also an important cause of TD in children, it seems to be under-recognized; only two children with metoclopramide-induced TD are reported in the literature [Putnam et al, 1992; Mejia and Jankovic, 2005a]. *More prospective or retrospective cohort studies are needed to determine the true prevalence of metoclopramide induced TD in children*.

CONCLUSIONS

- *Atypical antipsychotics may be better alternative medications with less risk of causing TD and should be considered whenever possible*. In long-term studies, the incidence of TD due to first-generation antipsychotics was reported to be 5% per year in adults and 25-30% in elderly patients, while the incidence of TD due to second-generation antipsychotics was 0% in children and 6.8% in the mixed adult and elderly population [Correll, 2004].

- *TD may have not only medical, but also legal implications*. Although avoiding DRBD is the best approach to minimizing this risk, physicians must be able to recognize the early symptoms and signs of TD in patients exposed to DRBD and provide appropriate management. When a patient develops TD, withdrawal of the offending drug should be the first management strategy. If this strategy fails, various pharmacological treatments may be considered, including TBZ, a monoamine-depleting drug by inhibiting the central vesicular monoamine transporter type 2 [Jankovic and Beach, 1997; Vuong et al, 2004].

- *More research is needed to develop new medications* that, without dopamine receptor antagonism, are able to treat conditions in which DRBD are currently employed.

REFERENCES

1) Correll CU, Leucht S, 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.
2) Fernandez HH, Friedman JH. Classification and treatment of tardive syndromes. The Neurologist 2003; 9:16-27.
3) Ganzini L, Casey DE, Hoffman WF, McCall AL. The prevalence of metoclopramide-induced tardive dyskinesia and acute extrapyramidal movement disorders. Arch Intern Med 1993;153:1469-1475.
4) Jankovic J, Beach J. Long-term effects of tetrabenazine in hyperkinetic movement disorders. Neurology 1997; 48:358-362.
5) Jankovic J. Tardive syndromes and other drug-induced movement disorders. Clinical neuropharmacology 1995;18:197-214.
6) Mejia NI and Jankovic J. Tardive dyskinesia and withdrawal emergent syndrome in children. 2005b [Submitted].
7) Mejia NI, Jankovic J. Metoclopramide-induced tardive dyskinesia in an infant. Mov Disord 2005; 20:86-89a.
8) Miller LG, Jankovic J. Metoclopramide-induced movement disorders. Arch Int Med 1989;149:2386-2392.
9) Paulson GW. Historical comments on tardive dyskinesia: a neurologist's perspective. J Clin Psychiatry 2005;66:260-264.
10) Putnam PE, Orenstein SR, Wessel HB, Stowe RM. Tardive dyskinesia associated with use of metoclopramide in a child. J Pediatr 1992;121:983-985.
11) Rodnitzky RL. Drug-induced movement disorders in children and adolescents. Expert Opin Drug Saf. 2005;4:91-102.
12) Stacy M, Jankovic J. Tardive dyskinesia. Current Opinion in Neurology and Neurosurgery 1991;4:343-349.
13) Tonini M, Cipollina L, Poluzzi E, Crema F, Corazza GR, De Ponti F. Review article: clinical implications of enteric and central D2 receptor blockade by antidopaminergic gastrointestinal prokinetics. Ailment Pharmacol Ther. 2004;19:379-390.
14) van Os J, Fahy T, Jones P, et al. Tardive dyskinesia: who is at risk? Acta Psychiatr Scand. 1997; 96:206-216.
15) Vuong K, Hunter CB, Mejia N, Jankovic J. Safety and efficacy of tetrabenazine in childhood hyperkinetic movement disorders. Mov Disord 2004;19(Suppl 9):S422.
16) Woerner MG, Alvir JM, Saltz BL, Lieberman JA, Kane JM. Prospective study of tardive dyskinesia in the elderly: rates and risk factors. Am J Psychiatry 1998; 155:1521-1528.
17) Wonodi I, Helene MA, Cassady SL, Sherr JD, Avila MT, Thaker GK. Ethnicity and the course of tardive dyskinesia in outpatients presenting to the motor disorders clinic at the Maryland Psychiatric Research Center. J Clin Psychopharmacol 2004; 24: 592-598.

Disclosures: None.