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 in patients referred to a movement disorders clinic. **BACKGROUND:** Tardive dyskinesia (TD), a hyperkinetic movement disorder causally related to dopamine receptor blocking drugs (DRBD), is a well-recognized iatrogenic disorder. Although 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. **RESULTS:** We report data on 434 patients listed in our database for whom we have detailed clinical information. The patients (334 female, 77.0%), had a mean age of 63.8 ±14.8 years at their initial evaluation. A causal DRBD was well defined in 411 (94.7%) patients. The most common medications associated with the onset of TD were haloperidol (N=191, 18.4%), metoclopramide (N=171, 16.5%), the combination of Amitriptyline and Perphenazine (N=85, 8.2%), and thioridazine (N=72, 6.9%) [Figure 2]. **CONCLUSIONS:** 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 temporally 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, 2005]. 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; Pasricha et al, 2006] [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, Table 3]. 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, 2007]. 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. Some conditions that may require DRBD therapy

Gastroenterological	Nausea, vomiting, GERD, diabetic gastroparesis, gastrointestinal imaging.
Psychiatric	Anxiety, depression, schizophrenia, bipolar disorder, alchoholism.
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)
b.Piperidine	Triflupromazine (e.g. Vesprin)
c.Piperazine	Thioridazine (e.g. Mellaril)
	Mesoridazine (e.g. Serentil)
	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
	Clebopride
	Remoxipride
	Veralipride
	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. 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]. We excluded patients with drug-induced parkinsonism [Noyes et al, 2006]. Demographic and clinical data were ascertained. We also searched for information about dose, treatment duration, and drug free intervals.

RESULTS

We report data on 434 TD patients listed in our database for whom we have detailed clinical information. Patients, 334 female (77.0%), had a mean age of 63.8 ± 14.8 years at their initial evaluation. Of the 434 patients, the majority presented with orolingual stereotypy (N=198, 45.0%), dystonia (N= 165, 37.5%), or other stereotopies (N=159, 36.1%) [Figure 1]. The most frequent phenomenology that patients exhibited, alone or in combination with other TS, were orolingual stereotypies (N=292, 28.2%), dystonia (N=256, 24.7%), and other stereotypies (N= 253, 24.4%). A specific causal DRBD was defined for 411 (94.7%) patients. The most common medications associated with the onset of TD were haloperidol (N=191, 18.4%), metoclopramide (N=171, 16.5%), the combination of Amitriptyline and Perphenazine (N=85, 8.2%), and thioridazine (N=72, 6.9%) [Figure 2].

FIGURE 1. Tardive Syndromes Present in 440 Patients

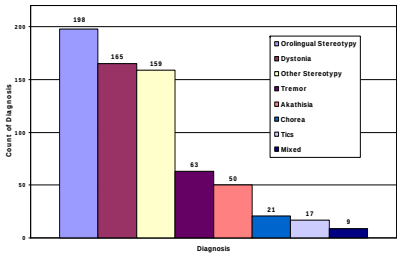


TABLE 3. Demographic and clinical characteristics of 434 TD Patients

Item	Characteristics
Sex	**100 (23.0%) male; 334 (77.0%) female**
Mean Age at initial evaluation	**63.8 years ± 14.8 (SD)**
DRBD indication	
Psychiatric	**68.2%**
Gastrointestinal	**30.0%**
Other	**1.8%**
Primary TD Type	
Orolingual Stereotypy	**45.0%**
Dystonia	**37.5%**
Other Stereotypies	**36.1%**
≥ 1 TD syndrome	**43.1%**

DISCUSSION

Despite the recognition of TD more than a half of century ago, the pathophysiology of this iatrogenic disorder is still not well understood [Marchand and Dilda, 2006]. 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].

DISCUSSION (cont'd)

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; Pierre, 2005]. Although atypical antipsychotics may be better alternative medications with less risk of causing TD, the risk of TD may increase with chronic use of these drugs, similar to the typical neuroleptics [Tarsy and Baldessarini, 2006]. 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 [Kenney and Jankovic, 2006]. More research is needed to develop new medications that, without dopamine receptor antagonism, are able to treat conditions in which DRBD are currently employed.

CONCLUSION

In this review of 434 patients referred to a movement disorders clinic with prior history of exposure to DRBD, the most common medications associated with the onset of TD were were haloperidol (N=191, 18.4%), metoclopramide (N=171, 16.5%), the combination of amitriptyline and perphenazine (N=85, 8.2%), and thioridazine (N=72, 6.9%). Prospective longitudinal studies are needed to confirm whether atypical neuroleptics have a lower risk for TD than the tradional typical neuroleptics.

FIGURE 2. Medications Associated with the onset of TD

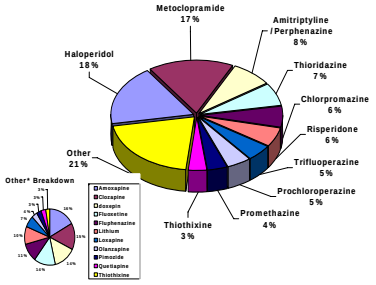
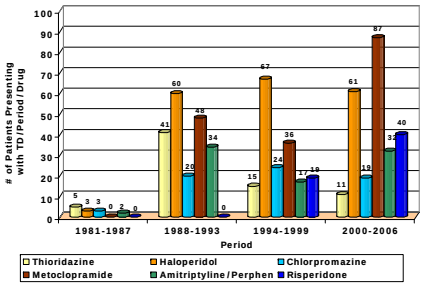


FIGURE 3. Drugs Associated with Tardive Dyskinesia



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Disclosures: None