The Efficacy and Safety of Fluphenazine in Patients with Tourette Syndrome

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Abstract

OBJECTIVE: To evaluate the safety and efficacy of fluphenazine in patients with Tourette syndrome (TS). BACKGROUND: Haloperidol and pimozide are the only neuroleptics currently approved by the FDA for the treatment of TS, but other neuroleptics have been used to treat troublesome tics. Although head-to-head, double-blind, comparative trials are lacking, our impression, based on long-term experience in a large number of patients, is that fluphenazine is at least as effective as the other neuroleptics with fewer adverse effects. DESIGN/METHODS: Patients diagnosed with TS according to the Tourette Syndrome Classification Study Group criteria, evaluated in our Movement Disorders Clinic between 12/14/1981 and 3/24/2004, were selected for this study if they were treated with fluphenazine for at least one year. Response to fluphenazine, the main outcome measure, was rated on a 1-to-5 clinical rating scale (1 = marked reduction in tics and improvement in function, 5 = worsening of tics and/or deterioration in function). All recorded complications were coded according to their likelihood of being fluphenazine related. RESULTS: Randomly selected 272 patient charts out of 1359 with TS were reviewed. Of these, 107 were treated with fluphenazine, 63 of whom (56 male) were treated for at least one year. Their mean age at initiation of fluphenazine was 15.6 ± 9.9 years (5.7-60.0) and the mean duration of fluphenazine treatment was 3.9 ± 3.3 years (range: 1.0-13.3). In 84.1% of patients the response to fluphenazine was rated as 1 or 2 (marked to moderate improvement). The following were the most frequent side effects attributed to fluphenazine: drowsiness (11), weight gain (5), dystonic reaction (5), akathisia (4) and depression (3). None of the patients developed tardive dyskinesia. Of 32 patients who temporarily discontinued fluphenazine, 27 (84.4%) experienced rebound worsening of symptoms. CONCLUSIONS: Our study provides evidence that fluphenazine is a safe and effective drug in long-term treatment of tics. Although a double-blind controlled study is needed to confirm the anti-tic efficacy of the drug, our longitudinal study indicates that the incidence of side effects, particularly tardive dyskinesia, in a population of young TS patients is very low.

Background

Tourette syndrome (TS) is a neurological disorder characterized by motor and phonic tics, often associated with neurobehavioral co-morbidities, such as attention-deficit, obsessive-compulsive disorders, and impulse-control problem [1,2]. Fluphenazine is a broad spectrum, long-acting piperazine phenothiazine, known to antagonize D2 dopamine receptors. Previous reports of fluphenazine in TS, including a placebo-controlled trial [3], have shown that fluphenazine has an equal or higher efficacy compared to haloperidol, with less sedation and fewer side effects [4-6]. Haloperidol has been reported to produce unacceptable side effects in about 84% of patients and therefore only a minority, 20-30%, of TS patients continues treatment for extended periods [7]. In a five-year study, 21 patients with multiple tic disorder, unable to tolerate haloperidol, were treated with fluphenazine; 16 of these patients reported fewer side effects with fluphenazine as compared to haloperidol and had either equivalent (N = 5) or better (N = 11) tic control [6]. In another report, side effects associated with neuroleptics, such as sedation, depression, weight gain and school phobia, were less frequent with fluphenazine than with haloperidol and other neuroleptics [8]. The primary goal of this study is to provide data on long-term safety and efficacy of fluphenazine in a large cohort of patients with TS.

Methods

All subjects (N = 1349) diagnosed with TS according to the criteria formulated by the Tourette Syndrome Classification Study Group [9] evaluated in the Movement Disorders Clinic, Baylor College of Medicine between 12/14/1981 and 3/24/2004 were considered candidates for this study. We randomly selected 272 patients for further analysis. The patients were grouped into one of the following categories: 1. never treated with fluphenazine; 2. tried on fluphenazine, but the drug was discontinued within the first year; 3. treated with fluphenazine for at least one year over the past 23 years. Furthermore, patients treated with fluphenazine for at least one year were subsequently categorized as currently still treated (ongoing treatment) or withdrawn from treatment (after one year). Response to fluphenazine, the main outcome measure, was rated on a 1-to-5 clinical rating scale (1 = marked reduction in tics and improvement in function, 5 = worsening of tics and/or deterioration in function) previously described [10]. All adverse events were recorded by one author (YS) onto case report forms and later entered into a database and coded according to their relationship to the study drug. After data from the first 40 charts were entered, an independent audit was conducted by the other investigators (KV and JJ) for quality assurance and to standardize interpretation of data that required clinical judgment.

Results

All data analysis was performed with SPSS v12. Demographic information, disease severity, treatment response, adverse event profile and reasons for discontinuation from or change during fluphenazine treatment among patients with TS are presented in Tables 1 - 4 and Figure 1.

Total of 63 patients (56 male), with mean age onset of TS symptoms was 8.3 ± 7.2 (ranging 1.2 - 60) and their mean age at initiation of fluphenazine was 15.6 ± 9.9 years (5.7-60.0). They were treated with fluphenazine for a mean of 3.9 ± 3.3 years (1.0-13.3). Response to fluphenazine (marked to moderate improvement) was rated as 1 or 2 in 84.1% of the patients. The mean daily dose was 3.9 ± 2.7 (ranging 1.0-12.0) mg per day. The following were symptoms attributed to fluphenazine: drowsiness (11), weight gain (5), dystonic reaction (5), akathisia (4), depression (3), lightheadedness (2), nervousness/anxiety (2), nausea/vomiting (2), dizziness (1), orthostatic hypotension (1), and panic attacks (1). Also one patient had slightly abnormal liver functions, which did not require the discontinuation of the treatment. None of the patients developed tardive dyskinesia. Twenty-three patients discontinued the drug for the following reasons: side effects (7), lack of efficacy (6), better results with botulinum toxin (2), and other reasons [Table 4]. Of the 32 patients who temporarily discontinued fluphenazine 27 (84.4%) experienced rebound worsening of symptoms.

TABLE 1. Demographic Information Among Patients with Tourette Syndrome Receiving Fluphenazine Treatment for More than One Year (N = 63) [a,b]

	Ongoing (n = 39)		Withdrawn (n = 23)	
	Mean (SD)	Range	Mean (SD)	Range
Age at symptom onset (yr)	7.3 (4.5)	1.2 – 24.5	9.8 (10.5)	2.1 – 60.0
Age at initial fluphenazine treatment (yr)	14.4 (7.3)	5.7 – 37.2	17.7 (13.3)	7.3 – 60.0
Duration of fluphenazine treatment (yr)	4.5 (3.8)	1.0 – 13.3	3.0 (1.9)	1.0 – 9.6
Dose at last visit (mg/d)	3.8 (2.5)	1.0 – 10.0	4.1 (3.1)	1.0 – 12.0

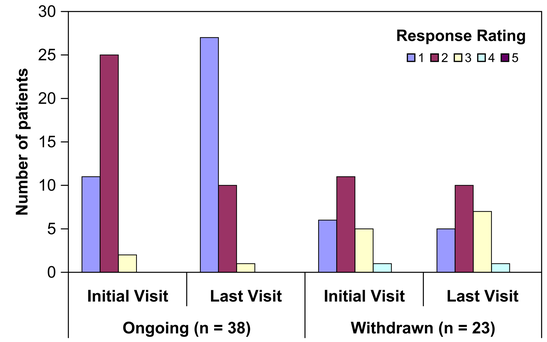
[a] Data for 1 patient was lost to follow-up after one year
[b] All group comparisons were non-significant, $p > 0.05$

TABLE 2. Disease Severity at the Initial and Last Evaluation

Fluphenazine treatment	n	Disease Severity: Mild	Moderate	Severe	Disabling
Initial evaluation [a]					
Ongoing	39	0	6	33	0
Withdrawn	23	0	1	22	0
Last evaluation [b]					
Ongoing	38	1	6	31	0
Withdrawn	23	1	1	20	1

[a] $\chi^2 = 0.03$, $p = 0.19$
[b] $\chi^2 = 0.06$, $p = 0.33$

FIGURE 1. Response to Fluphenazine Treatment for More Than One Year Among Patients with Tourette Syndrome



1 = Marked reduction in abnormal movements, excellent improvement in function
2 = Moderate reduction in abnormal movements, very good improvement in function
3 = Moderate reduction in abnormal movements, only mild or no improvement in function
4 = Poor or no response in abnormal movements or function
5 = Worsening of the movement disorder and/or deterioration in function

TABLE 3. Adverse Event Profile Among Patients with Tourette Syndrome Receiving Fluphenazine Treatment

Adverse Event [a]	# of events reported	N (62)	Dose reduction [b]	Patient D/C
Drowsiness/fatigue	11	11	2	4
Weight gain	5	5	1	1
Akathisia	5	4	4	0
Depression	3	3	1	1
Dystonic reaction/oculogyric crises	5	5	1	3
Elevated Liver Function tests	1	1	0	0
Lightheadedness	2	2	0	0
Nervousness/anxiety	2	2	0	1
Nausea/vomiting	2	2	0	1
Dizziness	1	1	0	0
Orthostatic hypotension	1	1	0	0
Panic attacks	1	1	0	0
Rolling eyes	1	1	0	1
None reported	—	41	—	—

[a] Fluphenazine causality = Possible or Probable
[b] Per event reported

TABLE 4. Reasons for Change or Discontinuation of Fluphenazine Treatment Among Patients with Tourette Syndrome (N = 63)

	Ongoing (39)	Withdrawn (23) [a]	p
Reason for Change			
Side effects	3	1	1.00
Lack of efficacy	0	5	0.003 *
Movement disorder spontaneously resolved	3	0	0.29
Death (unrelated to fluphenazine)	0	0	-
Travel/financial reasons	0	0	-
Better results with botulinum toxin	0	1	0.37
Miscellaneous	15	4	0.10
Lost to follow-up	0	0	-
Reason for Discontinuation			
Side effects	0	6	0.002 *
Lack of efficacy	0	7	0.0005 *
Movement disorder spontaneously resolved	0	1	0.37
Death (unrelated to fluphenazine)	0	0	-
Travel/financial reasons	0	0	-
Better results with botulinum toxin	0	2	0.13
Miscellaneous	5	5	0.48
Lost to follow-up	0	1	0.37

[a] For the withdrawn group as reason for discontinuation, one patient was not available.

Discussion

Overall fluphenazine is a safe and effective drug for long term treatment of tics. Since haloperidol and pimozide currently are the only neuroleptics approved by the FDA for the treatment of TS [7], the results of our study highlight a need for double-blind controlled studies to confirm the anti-tic efficacy and safety of the drug. Our longitudinal study indicates that the incidence of side effects, including tardive dyskinesia, in a population of young TS patients is very low. While acknowledging the limitations of a retrospective study, our findings represent the long-term clinical experience in a large number of patients. Based on our longitudinal findings of high degree of efficacy and relatively low frequency of adverse effects, we now consider fluphenazine as the first line anti-tic pharmacotherapy. Although other neuroleptics have been reported to cause tardive syndromes in patients with TS [11-16], we have not encountered any case of tardive dyskinesia, one of the most feared side effect of chronic neuroleptic therapy, in our population of young TS patients treated with fluphenazine. Nevertheless, it is a prudent medical practice to caution patients and their caregivers about this and other potential complications and to follow such patients carefully to detect as early as possible any potentially serious adverse effects.

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