

## TEN YEAR OUTCOME OF TARDIVE DYSKINESIA DURING CONTINUOUS TREATMENT WITH FIRST GENERATION ANTIPSYCHOTICS

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### SUMMARY

**Objective:** The aim of this study is to determine the course of tardive dyskinesia (TD) during continuous medication with first generation antipsychotics.

**Subjects and methods:** Patients of a psychiatric nursing home were assessed for TD by means of the AIMS on two occasions ten years apart.

**Results:** Out of 10 patients who met criteria for TD at baseline the global judgement of severity of the AIMS improved in 5, worsened in 4 and remained unchanged in one patient. The mean sum score of the AIMS slightly increased from 5.5 to 6.3. No patient developed movements that incapacitated him in his daily activities.

**Conclusion:** In concordance with the available literature these findings support the view that under continuous treatment with antipsychotics there is an equal chance for improvement as for deterioration. Progressive worsening to severe forms of TD was not observed.

**Key words:** Drug-Induced Dyskinesia - tardive dyskinesia - long-term course – Antipsychotics - Psychiatric Nursing Home

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### INTRODUCTION

Tardive dyskinesia (TD) is considered to be the most severe side effect of antipsychotic medication, since it may be irreversible and may lead to permanent impairment (Sachdev 2000). Introduction of second generation antipsychotics has ameliorated but not abolished the problem (Tarsy & Baldessarini 2006). Discontinuation of antipsychotics "would obviously be the ideal treatment" (Kane et al. 1992) yet puts the patients at risk for relapse. Actually in most patients TD is of minor severity so that the patients are not bothered by it and sometimes are not even aware of it. In these prevailing cases of minor severity most clinicians find it inappropriate to put at stake a good remission of psychosis for the sake of a minor movement problem and therefore opt for continuing the antipsychotic medication. Yet the question arises whether the process that has led to the movement disorder may continue, turning a minor problem into a major one with debilitating consequences.

The aim of this study is to find out whether patients with TD maintained on antipsychotics have to expect further deterioration of TD or not. The author had the opportunity to make his own observations over a ten year period in patients of a psychiatric long-term care facility.

### SUBJECTS AND METHODS

Patients of a psychiatric nursing home were assessed for TD on two occasions ten years apart (1985/86 and 1995/96). Patients older than 75 years at baseline and bedridden patients were excluded from evaluation.

Since it seemed appropriate to include also minor forms of TD in this longitudinal study we choose the more sensitive criteria for TD proposed by Jeste and Wyatt (Jeste & Wyatt 1982) (prevalence of a severity of 2 (mild) on the AIMS in at least one body region). Chlorpromazine equivalents (CPZE) were calculated for orally administered drugs and depot drugs according the data of Rey et al. (1989) and Schulz et al. (1989). All ratings were performed by the author.

Statistical evaluations were done with student's t-test for continuous variables and with chi-square tests with continuity correction for nominal variables.

## RESULTS

At baseline the sample consisted of 67 patients (mean age 65.2 years, 42% males) of whom 25 (37%) met the criteria for TD. Mortality in these aged and severely ill patients was high over the 10-year period so that 13 out of 25 patients with TD at baseline (52%) had died by the second assessment leaving 12 patients who could be assessed on both occasions. Two patients had not received antipsychotics continuously and were excluded from further evaluation. The remaining 10 patients (mean age 67.5 years, 60% males) had received moderate and fairly stable doses of antipsychotics throughout the period (baseline 292 CPZE, follow-up 271 CPZE). Since this study was started in 1985, only first generation antipsychotics (including clozapine) were used. Diagnostically there were 4 patients with schizophrenia (according to ICD-10) and 6 with various forms of mental brain syndromes.

Medications and AIMS scores of these patients are presented in table 1. Global judgement of severity of TD, which was based on the highest single score of the items (Munetz und Benjamin 1988) improved in 5 patients (2 of them not reaching the threshold for TD any more), worsened in 4 patients and remained unchanged in one patient. Comparing the sum scores of the AIMS at the two points of time there was almost no change in the score for the bucco-linguo-masticatoric area, a slight increase in the scores for the trunk and the extremities and a slight increase in the overall sum scores. None of the patients were impaired in breathing or swallowing or otherwise incapacitated in their daily activities. Even in the patient with the highest increase in the AIMS sum score (pat. No 4, +11) the pattern of movements was not rated as incapacitating.

A comparison between deceased and surviving patients was performed to rule out bias through premature death of patients with more severe TD. Deceased patients were significantly older (68.2 vs 56.9 years;  $p < 0.000$ ) and had received a lower mean dose of antipsychotics (148.5 vs 326.4 CPZE;  $p < 0.001$ ). Prevalence of TD was somewhat higher in deceased patients (44% vs 31%; ns), yet severity of TD was lower in deceased patients than in surviving patients (3.6 vs 4.0 points on AIMS; ns).

## DISCUSSION

Given the different ways of measuring the outcome there was no evidence for a general trend towards worsening of TD over the ten year period. Overall sum scores of the AIMS slightly increased whereas according to the global judgment of severity more patients improved than deteriorated. Since patients had grown ten years older between assessments and higher age is an independent risk factor for dyskinesic movements (Saltz et al. 1991, Woerner et al. 1998) an increase in severity of TD just for this reason would not have been surprising.

Fortunately there was no single patient in whom TD had progressed to severe and debilitating symptoms. In this respect the ambiguous role of antipsychotics might be of importance, since these drugs may cause TD but also are capable of suppressing these movements. Suppression of TD with D2 receptor blocking agents is one possible treatment (Gupta et al. 1999, Margolese et al. 2005, Sachdev 2000) which

works in some patients when other strategies fail, but leaves some doubt as to whether this treatment will cause further impairment in the long run. In one of our patients (no. 6) tiapride was added to the clozapine therapy and was maintained for 7 years until the follow-up examination. Tiapride not only improved the symptoms of TD but this improvement has held stable over the years.

**Table 1.** 10 patients with TD: medications and AIMS scores (BLM: bucco-linguo-masticatoric area; T/E: trunk and extremities; sum: sum score; AIMS T2-T1: difference between assessments, positive score indicating increased severity)

P.at. No	Medication	Baseline (T1)				Follow-up (T2)					AIMS T2 – T1
		Global severity	AIMS			Global severity	AIMS				
			BLM	T/E	Sum	Medication		BLM	T/E	Sum	
1	Haloperidol 3mg	2	5	0	5	Haloperidol 2mg	3	7	0	7	+2
2	Fluphenacine 2mg	2	3	0	3	Clozapine 125mg	3	7	3	10	+7
3	Haloperidol 3mg	3	5	0	5	Haloperidol 1.5mg Chlorprothixene 50mg	1	3	1	4	-1
4	Zuclopenthixol 50mg	2	3	0	3	Zuclopenthixol 50mg	3	7	7	14	+11
5	Flupentixol 2mg	3	8	0	8	Flupentixol 2mg	2	3	0	3	-5
6	Clozapine 400mg	3	4	6	10	Clozapine 200mg, Tiapride 300mg	2	2	0	2	-8
7	Clozapine 150mg Zuclopenthixol 25mg	3	2	3	5	Zuclopenthixol 25mg	4	4	4	8	+3
8	Fluphenacine 3mg Chlorprothixene 50mg	3	6	2	8	Fluphenacine 1mg Chlorprothixene 50mg	2	5	1	6	-2
9	Zuclopenthixol 55mg	3	5	0	5	Zuclopenthixol 55mg	3	6	1	7	+2
10	Thioridazine 400mg	2	3	0	3	Thioridazine 200mg	1	2	0	2	-1
	Mean		4.4	1.1	5.5			4.6	1.7	6.3	

**Table 2.** Studies on the course of TD under continuing antipsychotic medication for periods of more than 3 years

Author	Year of publication	years to follow-up	N	No TD <sup>§</sup>	Status of TD at follow-up		
					Better <sup>§</sup>	unchanged	worse
Bergen et al. (1989)	1989	4	53	9 (17%)			
Chouinard et al. (1988)	1988	5	38	9 (24%)			
Fernandez et al. (2001)	2001	14	53	33 (62%)	2 (4%)	8 (16%)	10 (19%)
Fornazzari et al. (1989)	1989	5	22		7 (32%)	11 (50%)	7 (32%)
Gardos et al. (1994)	1994	10	19	11 (58%)			
Itoh & Yagi (1979)	1979	5	14		12 (86%)	2 (14%)	0
Koshimo et al. (1991)	1991	11-12	28		5 (18%)	15 (39%)	8 (21%)
McClelland et al. (1991)	1991	16	11*	3 (27%)			
Mehta et al. (1977)	1977	5	6*	2 (33%)		3 (50%)	1 (17%)
Miller et al. (1995)	1995	10	8	5 (63%)		3 (37%)	
Robinson et al. (1986)	1986	3.5	31*	15 (48%)			
Yagi & Itoh (1985; 1987)	1987	10	9*	6 (67%)		3 (33%)	0
Yassa & Nair (1992)	1992	10	32 <sup>1</sup>		6 (19%)	18 (56%)	8 (25%)
			12 <sup>2</sup>		3 (25%)	4 (33%)	5 (42%)
Sum (mean %)				93 (44%)	35 (22%)	67 (36%)	39 (22%)
Total of improved patients					128 (38%)		

\*Numbers recalculated after exclusion of patients without antipsychotics

<sup>§</sup>Depending on the data presented either recovered or improved patients or both are listed

<sup>1</sup>Patients with antipsychotic dosage unchanged

<sup>2</sup>Patients with antipsychotic dosage decreased

The present study has several limitations, mainly the small number of cases and a drop-out rate of more than 50% percent due to deaths during the ten year period. On the other hand the long period between assessments allows us to assess the effects of antipsychotics in the long term. Comparisons between deceased and surviving patients showed no significant differences concerning severity of TD and medication. A bias caused by drop-outs cannot be ruled out but seems not very likely. Of course it was not possible to maintain medication unchanged in all cases over the entire period, but changes were modest (table 1) and of minor significance. It is a strength of this study that patients received their medication under supervision over the entire period and that they lived in stable surroundings.

Due to the small sample our conclusions can only be tentative, but our findings seem worth reporting because data on this subject is scarce. We reviewed the literature for studies which investigated the course of TD over periods of more than three years. Table 2 summarises those reports providing data for patients receiving continuous medication with predominantly first generation antipsychotics and displays information on improvement and worsening of TD. Since methodology differed considerably sometimes incomplete data are supplied. Some studies only reported on improvements for which different outcome measures were applied (total remission or improvement or both). We found 13 studies covering 336 patients of whom 128 (38%) were considered improved (no TD or reduced severity). Worsening of TD was observed in 22%. Findings in our patients are in line with these other reports and strengthen the view that TD with continuing antipsychotic medication is not necessarily a continually worsening process (Egan et al. 1997, Soares-Weiser & Rathbone 2006). On the contrary, far more patients got better than worse. Among those of our patients whose AIMS score increased the magnitude of deterioration was not clinically meaningful.

TD is still an enigma in many respects. The fact that it may be severely debilitating and persistent in some cases still makes it a matter of the utmost concern. Yet we apparently cannot predict which patients will be at risk of developing these severe cases of TD. The assumption, that a patient who has TD of minor severity will progress without fail to a more or most severe form if antipsychotic medication is continued is clearly not correct. One might propose the hypothesis that the risk of developing a severe form of TD is about the same in a patient with no signs of TD as in a patient with already existing TD of minor severity. It seems that TD of all kinds of severity manifests rather quickly and then tends to have a waxing and waning course with possible complete remissions.

All these data pertain for first generation antipsychotics. With second generation antipsychotics the situation might be even better as they induce less TD (Correll et al. 2004, Tarsy & Baldessarini 2006) and often ameliorate already existing TDs (Bai et al. 2003).

## CONCLUSION

Clinicians opting to continue antipsychotic medication despite TD in order to avoid psychotic relapse can expect that the risk they take is not as big as one might expect, even with first generation antipsychotics. There is a good chance that the use of second generation antipsychotics will give more favourable results (Soares-Weiser & Rathbone 2006). Larger prospective studies of this issue over prolonged periods are needed.

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