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Extrapyramidal Symptoms in 10 Years of Long Term Treatment of Schizophrenia: Independent of Psychopathology and Outcome

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Research Article**Extrapyramidal Symptoms in 10 Years of Long Term Treatment of Schizophrenia: Independent of Psychopathology and Outcome**Amresh Srivastava¹, Megan Johnston², Kristen Terpstra³, Larry Stitt⁴, Avinash De Sousa^{5*}, Nilesh Shah⁶¹Department of Psychiatry, Elgin Early Intervention Program for Psychosis, The University of Western Ontario, Ontario, Canada, and Mental Health Resource Foundation, Mumbai, Maharashtra, India,²Department of Psychology, University of Toronto, 100 St. George St., Toronto, Ontario, Canada, M5S 3G3³Department of Psychology, University of Western Ontario, London, Ontario, Canada N6A 5C1⁴Department of Epidemiology & Biostatistics, Schulich School of Medicine & Dentistry, The University of Western Ontario, London, Ontario, Canada N6A 5C1⁵Research Officer, Department of Psychiatry, Lokmanya Tilak Municipal Medical College, Mumbai⁶ Professor and Head, Department of Psychiatry, Lokmanya Tilak Municipal Medical College, Mumbai***Corresponding author**

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Abstract: One of the main arguments against prescribing first generation ‘typical’ antipsychotics is that extrapyramidal symptoms (EPS) can emerge as a side effect. EPS are distressing and interfere with the recovery and functioning of patients. Some of these symptoms persist over long periods of time, even after antipsychotic usage has been stopped. It is believed that second generation antipsychotics are less likely to cause EPS, which may aid in better functioning. We examined a cohort of patients of first episode schizophrenia, in a ten-year follow up study, for the presence of EPS. We assessed patients who had shown clinical recovery at the end of ten years of treatment. These patients were assessed for psychopathology using the PANSS, level of functioning by GAF, cognition by WMS and presence of EPS by AIMS. The present study show that abnormal EPS in first episode schizophrenia is present in 5% of patients at baseline, and 35.4% after 10 ten years. Patients in both groups of normal EPS and abnormal EPS showed equal clinical recovery on all parameters. Patients’ EPS symptoms at end point did not show any correlation with any end point clinical, social and cognitive parameters. We conclude that there is low incidence of EPS in the early phase of schizophrenia; however, EPS occur in about a third of all the patients after long term ten years treatment. EPS is not found to be correlated to level of psychopathology, and it does not correlate with any of the clinical and social outcome parameters.

Keywords: schizophrenia, extrapyramidal symptoms, psychopathology, antipsychotics

INTRODUCTION

Schizophrenia is a complex neuropsychiatric disorder. Antipsychotic drugs, which form the mainstream treatment of schizophrenia, often result in serious neurological side effects, particularly extrapyramidal symptoms (EPS) and tardive dyskinesia (TD), with about 30-35% patients experiencing these side effects in the short-term as well as in long term treatment [1]. EPS and TD have been reported in 21-30% patients of never-treated schizophrenia since the pre-neuroleptic era [2]; however, recent studies have reported a relatively lower incidence of 15 to 20%, in drug naïve and first-episode schizophrenia patients [3]. EPS in the early phase of schizophrenia is an important risk factor for later onset of EPS and TD, and a predictor for response to medication. The advent of second generation ‘atypical’ antipsychotics (SGA) gave hope for the possibility of a lower incidence of EPS, leading to better treatment compliance and outcome. In fact, the absence of EPS was one of the criteria for ‘atypicality’ of these molecules. While atypical antipsychotics may cause tardive dyskinesia, the percentage is usually significantly lower than with conventional typical antipsychotics. Using atypical

antipsychotics, particularly at lower doses, may aid in preventing symptoms of tardive dyskinesia in older adults [4].

Unfortunately, it soon became apparent that SGAs were not free from EPS, and that these symptoms eventually lead to discontinuation of treatment. A meta-analysis of 31 randomized control trials, which included 2320 patients, found no difference in risk of EPS between low potency first generation and second generation drugs [5]. Similarly, another study by Hasen et al. reported EPS in 65% of their sample despite three quarters of patients receiving SGA [6]. Therefore, EPS still continues to be a challenging problem in antipsychotic therapy. With respect to TD, a twelve-month incidence of probable or persistent TD, according to Schooler and Kane criteria, was 12.3% (N = 7). Subjects with TD did not differ from the rest of the sample regarding gender, race, duration of untreated psychosis, or baseline clinical characteristics [7].

EPS and TD have a number of determinants such as individual vulnerability of the patient, total neuroleptic exposure, age and gender, duration of

treatment, comorbidity, polypharmacy, early phase of illness and presence of neurological conditions. Despite a rich body of research, the exact mechanism of TD is not known. TD is a complex chronic and resistant movement disorder involving multiple neurotransmitter systems. It is likely to have a genetic basis as there are subgroups of patients who develop TD, and it is not exclusive to antipsychotic use but occurs in general population as well [8]. TD has a dose response and timeline relationship with antipsychotics, and a specific individual vulnerability across gender, ethnic group, and culture. It has a variable course, incidence, and for short, medium and long term exposure to neuroleptics [9]. Considering the risk for current and future TD, pharmacological treatment in the early phase of illness needs to be optimized in order to offer personalized medical care. On the other hand, EPS may not be a predictive factor for outcome; however, studies have reported that EPS is correlated with psychopathology and patients with EPS show poor response to treatment. The present study examines EPS in the early phase of schizophrenia and after treatment for long term follow up of 10 years.

METHODOLOGY

This study was conducted in a non-governmental psychiatric treatment center at Silver Mind Hospital, in Maharashtra, India. Ethics permission was approved by the local Independent Ethics Commission board. A total of 200 consenting patients of first episode schizophrenia (FES) diagnosed as per DSM III- R [10] criteria were recruited and followed up for 10 years. These subjects were untreated and in their first episode of schizophrenia, but not strictly drug naïve. All subjects were hospitalised. A naturalistic design was used, offering treatment as usual with limited availability of community case managers. The responsibility for community care was borne by the family members.

The patients were assessed for clinical, psychopathological, cognitive and functional parameters. EPS was assessed by Abnormal Involuntary Movement Scale (AIMS), psychopathology using the Positive and Negative Syndrome Scale (PANSS) and the Hamilton Depression Rating Scale (HDRS) [11-12]. Cognitive functioning was assessed by the Bender-Gestalt II (BG) and the Weschler Memory Scale (WMS) [13-14]. Level of functioning was assessed using the Global Assessment of Functioning (GAF) scale [15], and clinical recovery was measured by Clinical Global Impression scale (CGIS) [16]. Measurement of social outcome was conducted with a scale of independence level and employment status, using a locally developed measurement scale of 1-5 score. Assessments at baseline and at the end point were conducted by clinical research assistants who were trained in psychometric measurements. Patients available after 10 years of treatment were examined for

confirmation of diagnosis of schizophrenia as per DSM IV [17]. Of 107 patients, 101 re-consented for the study. These patients were re-assessed on the outcome parameters. The mean age of this sample was 28 years [SD=8.2: range 17-47] and 74 patients [73.3%] were male. At the end point, the mean age was 39.2 years [SD=7.9: range 22-58].

Inclusion and Exclusion Criteria

Inclusion criteria for the study were a diagnosis of schizophrenia as per DSM III-R, first hospitalisation, and informed consent for assessment. The exclusion criteria for potential study participants were substance abuse, outpatient or non-hospitalised individuals, evidence of significant previous treatment (antipsychotics for a period exceeding two weeks prior to hospitalisation), significant medical or neurological illness or the absence of objective information from the key relative. At the end point of ten years an inclusion criteria consisting of regular follow up, high level of compliance, availability of relative information, and an informed consent was applied.

Outcome Criteria

Primary outcome criteria were the presence of EPS, indicated by an AIMS score of greater than 2. Secondary outcome criteria were an increase in CGIS scores. Criteria for other parameters were: clinical improvement: scores equal to or less than 2, HDRS: scores less than 14, GAF: scores greater than or equal to 80, employment status: scores greater than or equal to 3, and independent living: scores greater than or equal to 3.

RESULTS

In our study, 77% of patients at the end of 10 years were taking SGA for at least 1 year duration. The antipsychotic drugs used were risperidone, olanzapine, quetiapine, clozapine, ziprasidone, or aripiprazole. About 30% patients were using more than one antipsychotic drug and received a mean daily dose of antipsychotics, within recommended limits of chlorpromazine equivalent of 300 to 600 mg per day.

This study shows that abnormal EPS are present in first episode schizophrenia at baseline in 5% (5 of 100) of patients, and at the end point after 10 years in 35.4% (35 out of 99) patients (6.3% vs. 34.3%, $p < .001$). Table 1 indicates no correlation between outcome parameters at baseline for both normal and abnormal EPS patients. In addition, both normal and abnormal EPS were not correlated with any of the clinical, social and cognitive parameters at the endpoint (Table 2). Patients in both groups of normal EPS and abnormal EPS showed equal clinical recovery on all parameters. Whereas, patients who had EPS symptoms at end point did not show any correlation with any end point clinical, social and cognitive parameters.

Table 1: Baseline association between EPS symptoms & Outcomes

	EPS≤2 (Normal) (n=95)	EPS>2 (Abnormal) (n=5)	P Value	Test
Clinical Outcomes:				
PS	28.4 (5.1)	25.6 (4.2)	.234	Unpaired t
NS	23.6 (6.9)	23.4 (6.9)	.958	Unpaired t
HDRS	17.6 (6.1)	18.6 (5.6)	.715	Unpaired t
PANSS	105.5 (14.1)	111.6 (8.4)	.343	Unpaired t
GAF	48.3 (11.2)	49.0 (8.2)	.884	Unpaired t
GP	54.6 (16.7)	46.8 (19.5)	.317	Unpaired t
BG	90.0 (13.8)	92.3 (6.1)	.776	Unpaired t
WMS	96.5 (12.7)	108.0 (8.5)	.128	Unpaired t
Social Outcomes				
Social - >3	9 (15.8%)	0 (0.0%)	>.999	Fisher's Exact
Suicidality >3	16 (17.8%)	0 (0.0%)	.585	Fisher's Exact

Table 2: 10 Years follow up association between EPS symptoms & Outcomes

	ES≤2 (Normal) (n=64)	ES>2 (Abnormal) (n=35)	P Value	Test
Clinical Outcomes				
Recovered	39 (60.9%)	20 (57.1%)	.713	Chi-square
PS	9.0 (4.1)	8.2 (3.6)	.321	Unpaired t
NS	12.0 (7.5)	13.1 (7.1)	.461	Unpaired t
HDRS	13.3 (5.8)	13.0 (4.1)	.823	Unpaired t
PANSS	52.3 (8.4)	50.1 (9.9)	.247	Unpaired t
GAF	77.3 (12.3)	81.2 (10.3)	.121	Unpaired t
GP	30.6 (11.2)	25.7 (12.4)	.048	Unpaired t
BG	98.9 (12.1)	98.0 (14.2)	.800	Unpaired t
WMS	91.1 (11.5)	88.6 (13.6)	.460	Unpaired t
Social Outcomes				
Social >3	14 (35.9%)	4 (20.0%)	.209	Chi-square
Productivity ≤3	33 (84.6%)	16 (80.0%)	.721	Fisher's Exact
Economic ≤3	17 (44.7%)	13 (65.0%)	.142	Chi-square
Education ≤3	31 (81.6%)	17 (85.0%)	>.999	Fisher's Exact
Exacerbation ≤3	22 (56.4%)	8 (40.0%)	.233	Chi-square

DISCUSSION

Our study shows two main findings. The first is that low incidence of EPS was found in the early phase of schizophrenia, and this significantly increases in long-term treatment. The second finding is that EPS is not correlated with psychopathology. Outcome on clinical and social parameters does not differ amongst patients with or without EPS in long term course. The study reconfirms earlier reported findings of high incidence of TD in schizophrenia and contrasts the finding of correlation with outcome. In our study only 5% patients were found to have EPS at the time of admission (in early phase of schizophrenia) which increased to 35% at the end of 10 years. The finding of low incidence of EPS is not in agreement with what has been reported in the literature. Generally, the incidence of EPS in both drug naïve and early phase of schizophrenia have been reported to be relatively high. Studies have described that abnormal EPS is present in about 5% to 23% patients, in first episode, drug naïve or never medicated schizophrenia (e.g. 16.9% by Chattererji *et al.*, and 7 %-11% by Gupta *et al.*) [18-20]. A higher incidence of EPS in long term treated subjects has been well

documented (e.g. 20-30% was reported by Addington *et al.*, and 0.5 to 70% by Gerlach and *et al.*) [21-22]. A landmark study from Mumbai in 1982 by Doongaji *et al.*, showed the prevalence of TD as 9% of a sample of 1,990 chronic patients of tertiary care hospital from the same city [23]. Another study, also from Mumbai, showed a prevalence of EPS due to acute administration of haloperidol ranging between 36-96% in a study of 76 subjects [24]. Yassa and Jeste analyzed data from 76 published studies on the prevalence of TD, which included a total of 39,187patients [25]. The reported prevalence ranged from 3 to 62 percent, with a mean of 24.2 percent Asian patients had lower prevalence of TD than North American, European, or African patients. It is unclear whether such a difference is primarily racial-genetic in origin or is due to external variables such as variations in diagnosis and treatment.

The low incidence of EPS in our sample can be due to a number of factors, such as shorter duration of illness (14 months), nature of psychopathology, low prevalence of negative symptoms and low level of antipsychotic prescribing by the community physicians.

Higher prevalence of TD in this study can be explained by 10 years of continued neuroleptic exposure, frequent changes in drug regime, chronicity, presence of residual symptoms, usage of more than one antipsychotic (40%) and anticholinergic drugs. The findings suggest that even a low incidence of EPS in the early phase of the illness (5%) is a significant risk for high incidence (34.3%) of EPS in long term course with antipsychotic treatment and therefore, antipsychotics with EPS potential should be carefully selected. EPS and TD have been reported to be correlated with clinical features and psychopathology of patients. Contrasting findings have been reported regarding correlation of TD and outcome of schizophrenia. Studies show direct correlation between courses, outcome and psychopathology. One study shows that, in the long-term treatment of schizophrenia, persons with TD have a significantly more severe and more refractory course of illness than those without TD, suggesting poorer prognosis and the need for specialized interventions [26]. Patients with TD, compared to those without TD, had significantly more severe psychopathology, were less likely to experience symptom remission, had more severe extrapyramidal side effects, and had lower levels of quality of life and functioning, lower productivity, and fewer activities (all $p < .001$) across the 3-year follow-up.

In our study we find that EPS was not correlated with any psychopathological factors, either at baseline or at the long-term follow-up. This finding is not in agreement with literature reports. Outcome was measured on clinical, (positive symptoms, negative symptoms, depressive features, cognitive features, level of functioning) and, social outcome, ability to live independently, ability to work and productivity. Patients with or without EPS did not differ on any of the outcome parameters after 10 years of treatment. It appears that EPS are independent of psychopathology in long term course of schizophrenia. Clinically, EPS is equally common amongst all domains of psychopathology in long term. CATIE reported that changes in PANSS scores were not significantly different, but patients with TD showed less improvement in neurocognitive scores. Schizophrenia patients with and without TD were similar in time of discontinuation of treatment for any cause, and improvement in psychopathology, but differed in neurocognitive response [27]. In another study, subjects with TD did not differ from the rest of the sample regarding gender, race, duration of untreated psychosis, or baseline clinical [28]. Our findings support the view that TD is not related to psychopathology and there is no difference in outcome between those with and without TD. These findings need to be confirmed in better designed prospective studies with frequent follow ups. Our results from this study only present incidence and its correlation with psychopathology in a cross-sectional manner. Despite

limitations, the present findings suggest the need for examining EPS as a pathological dimension.

We conclude that there is low incidence of EPS in the early phase of schizophrenia with about a third of all patients developing EPS after long term ten years treatment. EPS is not found to be correlated to level of psychopathology or any clinical or social outcome parameters.

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