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Analysis of Clinical Characteristics and Antipsychotic Medication Prescribing Practices of First-Episode Schizophrenia in Israel: A Naturalistic Prospective Study

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Abstract: Background: Investigation of the clinical presentation and treatment of first-episode psychosis is important in order to exclude effects of age, chronic illness, long-term treatment and institutionalization. The aim of this descriptive study was to investigate the management practices of first-episode schizophrenia in a cohort of patients in Israel and to document use of the various "typical" or "atypical" antipsychotic agents. *Method:* Fifty-one consecutive patients (26M, 25F) with first-episode psychosis were recruited for study participation and were administered either typical or atypical antipsychotic medications in a naturalistic manner. *Results:* While an approximately equal number of subjects received typical and atypical medications at illness onset, a prominent shift to atypical antipsychotic treatment occurred over the study course; 18 subjects had medication class shifts: 17 from typical to atypical, and one from atypical to typical. Negative symptoms did not affect length of hospitalization, but were associated with aggression. Higher depression rates were noted in patients with long hospitalizations who received typical antipsychotic medications. Immigrants were admitted at an age approximately four years older than native-born Israelis. *Conclusions:* The prominent shift from "typical" to "atypical" antipsychotic medications may indicate sensitivity of first-episode psychotic patients to side-effects of "typical" medications and prominence of use of atypical medications in this patient subpopulation be it due to improved efficacy over time or successful marketing. Unique cultural and population characteristics may contribute to the manifestation of first-episode psychosis and suggest the importance of more effective outreach to the immigrant population in order to manage an apparent treatment delay.

Introduction

Schizophrenia is a very debilitating and relatively common illness with a lifetime prevalence of approximately 1%. The disorder has significant morbidity associated with it, and an analysis of clinical symptomatology at first presentation of psychosis will assist in further comprehending the nature of the illness. Investigation of first-episode psychosis becomes important in order to exclude effects of age, chronic illness, long-term treatment and institutionalization (1). Results from a description of treatment response, relapse and side effect profiles may assist in the development of more competent and effective treatment schedules. In addition, a better understanding of the clinical, neurobiological, side effect and treatment response characteristics of first episode psychosis offers the intriguing possibility of predicting response and even modifying the illness at an early stage.

Previous studies have investigated characteristics of first-episode psychosis (e.g., 2-4), and have noted several important considerations. These include the importance of early identification and intervention (e.g., 5-8), the safety and efficacy of second generation antipsychotic medications (9), value of psychosocial interventions (10), the crucial determinant of "duration of untreated psychosis" for prognostic purposes (11), increased sensitivity to medication and side-effects (12), and the presence of cognitive dysfunction even at first presentation (13). In addition, several characteristic neurobiological factors have been noted to be present in first-episode psychosis including neuroimaging findings (e.g., 14). The quest remains to further describe and characterize unique aspects of the illness at first presentation

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and thus to further improve prospects of improving outcome (15).

The aim of this descriptive study was to investigate in a cohort of patients the management practices of first-episode schizophrenia in a naturalistic sense and to document use of the various "typical" or "atypical" antipsychotic agents.

Subjects and Methods

Study Organization

This naturalistic descriptive study was carried out at the Beer Yaakov Mental Health Center (Beer Yaakov, Israel). Consent for the investigation was obtained from the relevant Helsinki ethical standards committees. All patients signed informed consent following full description of the nature of the study to the patient as well as to family members when available. A research physician (RL) was principally responsible for study recruitment, evaluations and subject follow-up. Only inpatients during their initial first-episode admission were enrolled into the study.

Study Population

Patients considered eligible to participate in the study were between the ages of 18-55 and in their first episode of psychosis, required treatment with antipsychotic medication on a clinical basis for schizophreniform or schizophrenia disorder (as diagnosed according to DSM-IV criteria), and were no longer than five years since the beginning of the psychotic episode. Two board certified psychiatrists verified patients' diagnoses (RDS and RL) arrived at by means of a semi-structured interview according to guidelines of the Structured Clinical Interview for DSM-IV Axis I, Patient Edition (16). Subjects had to have been suitable to remain in the study for at least two years. Subjects entering the study were either male or female. Patients over the age of 55 were excluded in order to prevent the potential confound of late-onset illness. In addition, patients were excluded with any history of serious neurologic, medical or endocrine disorder as well as patients with any evidence of IQ less than 70. Patients with any medical contraindication to antipsychotic medication were also excluded from participation. Patients with a lifetime cumulative history of 12 weeks of treatment with antipsychotic medication for any reason were also excluded from the study.

Medications Administered

Patients were administered one of the following medications: typical antipsychotic medication (haloperidol, perphenazine, zuclopenthixol) or atypical antipsychotic medications (risperidone, olanzapine, clozapine).

Clinical Assessments

All study participants underwent extensive clinical and medication side-effect ratings every two weeks while enrolled in the study. These included the Positive and Negative Syndrome Scale (PANSS) (17), the Hamilton Scales for Depression and Anxiety (HAMD/A) (18, 19) and the Clinical Global Impression Scale (CGI) (20). Side-effect rating scales included the Barnes Akathisia Scale (BAS) (21), the Simpson-Angus Scale (SAS) (22) for extrapyramidal symptoms and the Abnormal Involuntary Movements Scale (AIMS) (20) for tardive dyskinesia. Furthermore, at baseline the Life History of Aggression scale (LHA) (23) was administered.

Results

Study Sample

Over a study recruitment period of approximately one-and-a-half years, 51 consecutive first episode psychosis subjects were recruited for study participation. Of the participants, 26 were male and 25 were female. Mean age of study participants was 28.75 (SD 7.84, range 18-53). Thirty-one (60.8%) of the subjects were native Israelis (born in Israel) and the rest were immigrants with a range of arrival dates into the country (mainly from the former USSR). Fifteen of the patients were married, five divorced, one common-law married and 30 were single. While the average age of the participants was 28.75 as noted above, the average age of appearance of psychotic symptoms (based on either patient self-report or precise information received from family members) in this subpopulation was 26.2 (standard deviation = 8.2). Thus the average duration of untreated psychosis may be reported as 2.55 years. Nine subjects

(17.6%) self-reported substance abuse with marijuana being the most prominently abused substance. While the age at first episode of psychosis was in the late 20s (males=29.4years, SD=7.8; females=28.2 years, SD=8; ns), 45 of the 51 subjects in the study (88%) had not completed high school.

Clinical Measures

See Table 1 for a summary of the clinical measures.

Table 1. *Clinical Rating Measures for First-Episode Schizophrenia Patients*

	mean	SD	Range	N
PANSS-Positive	21.71	6.37	12-38	51
Negative	17.06	7.07	7-43	51
General	36.78	11.55	19-84	51
Total	75.55	21.17	40-160	51
CGI	4.52	.91	2-6	50
HAM-D	14.00	7.94	0-32	42
HAM-A	10.02	6.45	0-22	42
LHA	6.18	8.61	0-34	38
SAS	10.12	.63	10-14	42
BAS	.21	.84	0-5	42

Length of Hospitalization

The length of hospitalization of subjects participating in the study ranged from one to 480 days (mean=46.3, SD=78.1). The mode period was three weeks to one month and the median 25 days. The length of hospitalization was categorized into short and long periods according to the median split.

Medications Administered

Table 2 describes the distribution of hospitalization and discharge medication. It can be seen that a shift to atypical neuroleptic treatment occurred over the course of the study. Twenty-five subjects did not change the drug class, seven remained with typical and 18 with atypical treatment. Eighteen subjects had medication class shifts: 17 from typical to atypical, and one from atypical to typical. The association between length of hospitalization and type of discharge medication was significant ($\chi^2_{(1)}$=4.00, p=0.045), indicating that the longer the hospitalization the more likely the patient was discharged on an atypical medication.

Average chlorpromazine equivalents at baseline was 168.56 (SD=62.94) and this dose was slightly increased during hospitalization and reached a level of 222.0 (SD=95.52). This increase was tested by paired t-test and indicated a significant difference (t=3.07, df=38, p=0.004). However, regardless of the general increase, the initial dose was not associated with the dose at discharge (r=0.12, p=0.46). Chlorpromazine level did not differ between patients treated with typical or atypical drugs (both p's > 0.80). Initial chlorpromazine level was not associated with any of the background variables (including age, gender, duration of untreated psychosis [DUP], and days of hospitalization), and clinical data. The only variable showing tendency to significant association was positive PANSS subscale (r=0.28, p=0.063), suggesting that higher medication doses were associated with more positive symptoms.

Table 2. *The Distribution of Antipsychotic Medication at Admission and Discharge (n, %)*

	Admission	Discharge
Typical		
zuclopenthixol	N=14, 27.5%	N=2, 3.9%
perphenazine	N=8, 15.7%	N=3, 5.9%
haloperidol	N=4, 7.8%	N=2, 3.9%
fluphenazine decanoate	N=0	N=1, 2.0%
Total	N=26, 50.9%	N=8, 35.7%
Atypical		
risperidone	N=19,37.3%	N=22, 43.1%
olanzapine	N=3,5.9%	N=11, 21.6%
clozapine	N=0	N=2, 3.9%
Total	N=22, 43.1%	N=35, 68.6%
Other		
benzodiazepine	N=1, 2.0%	N=0
No medication	N=2, 3.9%	N=8, 15.7%
Total	N=3, 5.8%	N=8, 15.7%

Associations between Clinical Measures

Associations were performed between baseline symptoms of schizophrenia (according to the three

subscales of PANSS) and other clinical data. To account for inflated Type-I error a correction of the critical alpha level was done according to the Bonferroni method resulting in a significance level of 0.0034. Significant associations were observed as follows: Higher baseline scores on the negative PANSS subscale were associated with higher scores on the LHA (r=-.44, p=0.006). Furthermore, higher baseline scores on the general PANSS subscale were associated with higher scores on the HAM-D (r=.65, p<0.001), and HAM-A (r=.57, p<0.001).

Change in Psychotic Symptomatology over Time

Change of PANSS measures was calculated for each patient. Table 3 summarizes the change of scores (percent) for all PANSS subscales. As could be seen, decrease of scores was more prominent with regard to the positive and general symptoms of schizophrenia. The change of PANSS scores was further analyzed according to a cut point of decrease of scores of 20% or more. Thus, patients showing a proportional change of 0.8 or less were considered as responders while patients with higher proportional change scores were defined as non-responders to the treatment. According to the 20% cut point 27 patients (87.1%) were defined as responders according to the positive symptoms; 9 patients (29%) responded according to the negative symptoms; 23 patients (74.2%) responded according to the general symptoms; and 22 (71.0%) were responders according to the total score. The response according to PANSS measures did not associate with the type of drug treatment. No differences of DUP were observed between responder and non-responder patients according to total PANSS change (p=0.41).

Table 3. *Percent Change in PANSS Rating Scale from Baseline*

	Mean	SD	Range
PANSS positive	56	18	19-100
PANSS negative	90	25	28-144
PANSS general	68	18	31-100
PANSS total	69	17	27-100

Side-Effects

Grouped t-tests were used to compare side effects, as reflected by the AIMS, SAS and BAS rating scales, of patients treated with typical and atypical drugs at baseline and discharge. No differences were noted (all p's > 0.23).

Associations between Length of Hospitalization and Symptomatology

The t-Tests were performed for differences in the level of symptoms of schizophrenia and CGI between subjects of short and long hospitalization periods. The critical alpha level was adjusted according to the Bonferroni method resulting in a significance level of 0.01. Subjects with a longer length of hospitalization showed higher baseline CGI scores (mean 4.9, sd=0.6) compared to subjects of short hospitalization periods (mean 4.1, sd=1.0) (t=3.44, df=48, p=0.001). In addition, subjects with long hospitalization periods showed higher baseline positive, general and total PANSS (positive: mean 19.6, sd=5.4; general: mean 41.0, sd=11.4; total: mean 83.6, sd=22.3) compared to those patients with shorter periods of hospitalization (positive: mean 23.9.6, sd=6.7; general: mean 32.7, sd=10.3; total: mean 67.8, sd=17.0) (positive t=2.52, df=49, p=0.015; general t=2.74, df=49, p=0.008; total t=2.85, df=49, p=0.006). No difference was noted on the baseline negative symptom subscales among these patients, i.e., the level of negative symptoms did not appear to affect length of hospitalization. Further analysis was explored using one-way ANOVA comparing subgroups of hospitalization periods. The analysis revealed that the baseline total PANSS was higher in subjects with hospitalization periods between one and two months (mean 97.7, sd=24.9), significantly higher than all other groups. These subjects had the highest scores on all of the PANSS subscales.

No associations were observed between hospitalization period and type of medication administered or any background demographic variables.

The association between gender and hospitalization period on the clinical measures was tested using 2×2 ANOVAs. A tendency to significant interaction was observed on the baseline negative PANSS (F=3.29, df=1,47, p=0.076). Post hoc (Duncan) revealed that among male subjects longer hospitaliza-

tion was associated with higher scores on the negative PANSS subscale (p=0.03), while among female subjects no difference was seen between long and short periods of hospitalizations.

The association between the initial administered medication at admission and hospitalization period on clinical measures was tested using 2×2 ANOVAs. No associations were noted. The association between the final medication at discharge and hospitalization period on clinical measures was tested using 2×2 ANOVAs. A significant interaction was found on the HAM-D score (F=4.30, df=1,32, p=0.046). Post hoc analysis revealed higher depression in patients with long hospitalizations compared to those with short hospitalizations who received typical antipsychotic medications (p=0.06). No difference was noted in patients receiving atypical antipsychotic medications.

Logistic regression models were performed on the two outcome measures of hospitalization period (1-25 days, 26+ days), and the response according to 20% improvement of the total PANSS score. The initial model included the following independent variables: age, DUP, baseline chlorpromazine equivalents, CGI, LHA, HAM-A, HAM-D, and the PANSS subscales. Missing values on some of the predictors resulted in a restriction of the analysis to 21 patients only. Therefore, the predictors were reduced to age, baseline chlorpromazine equivalents, CGI, HAM-A, HAM-D, and the PANSS subscales (DUP and LHA removed). The initial analysis performed on the hospitalization period did not yield any significant predictors. The restricted analysis was performed on 37 patients. Two predictors showed significant contribution to the prediction model: chlorpromazine equivalents, and CGI leading to an increase of 21.62% of the correct prediction. The initial analysis performed on the total PANSS change did not yield any significant predictors. The restricted analysis was performed on 27 patients. Two predictors showed significant contribution to the prediction model: age, and PANSS-positive leading to an increase of 14.82% of the correct prediction.

Interaction effect of medication and gender

Effects of the initial drug treatment (typical, atypical) and gender were tested with the attempt to find differential drug effects on the clinical data. A gender by drug interaction was observed on the total PANSS (F=4.49, df=1,45, p=0.04). This effect was due to higher PANSS in males receiving atypical (mean=80.2) compared to typical (62.3), while in females higher PANSS was seen in typical (80.7) compared to atypical (67.2). Post hoc (Duncan) analysis failed to reveal significant differences between groups.

A gender by hospitalization-drug interaction was observed on HAM-A (F=7.83, df=1,37, p=0.008). Post hoc (Duncan) tests showed that females receiving atypical drugs showed less anxiety (mean=4.4), compared to males who received atypical (12.1) (p<0.01), and females receiving typical drugs (12.1), p<0.01).

A tendency to gender by discharge-drug interaction was observed on LHA (F=3.30, df=1,30, p=0.08). Male and females receiving typical, but not atypical antipsychotic medication differing in their aggression levels (males=11.5, females=1.5; p=0.065).

Immigration effects

Immigration effects were tested, comparing native Israelis to immigrants on demographic and clinical measures. Interestingly, only age at onset showed a tendency to significant difference (native Israelis: mean=27.1, SD=6.7; immigrants: mean=31.3, SD=8.7; t=1.96, df=49, p=0.056). Other variables did not differ between the groups.

Discussion

While the incidence of schizophrenia remains fairly similar internationally, various aspects of the presentation and management of the illness may be expressed uniquely in different cultures and countries around the world. The description and characterization of such differences or similarities becomes important in order to prioritize mental health care delivery and to prioritize aspects of this psychiatric care for particular needs required. While this study does not promise to necessarily identify or characterize anything particularly new about the illness of schizophrenia or even the first episode expression of the disorder, it does illuminate several interesting aspects of the expression of a cohort of patients with

schizophrenia in Israel with a first-episode presentation of the disorder. These aspects include the observation of an equal male and female presentation even at the stage of first hospitalization. This specific observation is particularly interesting considering the general observation of increased hospitalization among males compared to females (24). A further interesting observation was the relatively high number of married subjects. While speculative, this may be accounted for by the traditionally close knit and supportive nature of many aspects of Israeli society and familial life thus allowing for familial and communal support once married despite potential diminished functioning resulting from an underlying prodromal or active psychotic illness as well as by the often young marital age in Israel.

Study observations indicated relatively low substance abuse levels for first-episode psychotic patients compared to other studies describing the incidence of substance abuse in similar populations (25). However, these levels of substance abuse as noted in this study are relatively high for Israel in general. This may be explained by the increased accessibility and use during the past few years of illicit substances in Israel, as well as by the increased use by schizophrenia patients in general (26, 27) including first-episode patients (28). The study results indicated a relatively long duration of untreated psychosis (3.4yrs). Although in this study a longer DUP was not associated with worse treatment response, others have noted that a longer duration of untreated psychosis may be a poor prognostic feature at least in the short term with respect to time to treatment response (29). This is a most unfortunate observation and more attention is required in order to identify these patients at an earlier stage and thus improve overall time to treatment response.

The association of negative symptoms with aggression, albeit in a first episode sample, confirms other studies, but not all (30, 31) who have reported a similar finding (32). In addition, clozapine, which is considered by many to be the most effective medication in the amelioration of negative symptoms, has also been reported to be very effective in decreasing physical and verbal aggression (33).

A very prominent shift from "typical" to "atypical" medications was noted to the extent that while there was an approximately equal spread of medication at initial use, at discharge most of patients had been either maintained on atypical medications or had been switched to atypical medication from typical medications. This is important considering that this observation took place in a naturalistic treatment setting. This observation may indicate the sensitivity of first episode psychotic patients to side-effects of "typical" medications (12), most notable of extrapyramidal nature. It does indicate a prominent use of atypical medications in this subpopulation of schizophrenia patients in Israel. Whether this use is due to increased efficacy of this class of medications or rather to successful marketing of these medications in this subpopulation of patients remains unknown due to the context of this epidemiological study (13, 34, 35). It is interesting to note that the response according to PANSS measures at discharge did not associate with the type of drug treatment.

The findings confirm those of others (4) indicating severity of illness and symptomatology at baseline to be directly correlated with outcome measures such as length of hospitalizations. In addition, it is important to note that, while most of the patients concluded their hospitalization on atypical medications, length of hospitalization (mean of 46 days) was not correlated with any subtype of typical or atypical medications. Thus, medications were equally effective with respect to length of hospitalization and appeared only to differ with respect to side-effect profile and treatment choice by treating staff. However, an increased length of hospitalization was noted in males who had higher ratings of negative symptoms. This is in keeping with several other studies that have also recognized and noted that more severe illness as reflected in a longer time to treatment response being associated with increased negative symptoms (36). That this was noted particularly in males also corroborates other studies which have noted similar observations and which have suggested that more severe illness in schizophrenia is present in males who also appear to present more negative symptoms of the illness (37). The length of hospitalization becomes an important measure of illness morbidity, not only in terms of economic burden and being indicative of overall more severe illness and thus treatment refractoriness, but also importantly with respect to patient suffering as in-

dicative in the tendency to significance of increased depression noted in those with longer hospitalizations. This may in turn be reflected hypothetically in increased suicide rates, although not noted in our study. What is important to note from these findings is that negative symptoms, at least in this study, do not appear to affect time to treatment response. What, however, did appear to affect length of hospitalization in the clinical presentation was the level of depressive features. This particular observation suggests that more attention be given to these symptoms in first-episode psychosis.

A particularly interesting finding of the study was the observation of an increased age at onset of illness (approximately four years) in immigrants compared to native Israelis. It remains unclear whether this difference may be accounted for by self-report bias, a longer duration of untreated psychosis, or differences in the nature of the illness in the immigrant population (including factors such as resilience, etc.). Since some of these factors may have prognostic implications, further research in this subpopulation of patients would be important in order to address this health issue among immigrants.

In conclusion, the expression of first-episode psychosis remains an important stage of the illness during which early intervention is crucial. In this cohort of patients in Israel, gender differences appeared minimal and substance use levels of concern. At hospital discharge, the vast majority of subjects were being administered "atypical" antipsychotic medications despite equal administrations of the two subtypes of medications at initial presentation. In light of recent more robust critical questioning and rethinking of the wide-spread use of atypical antipsychotic medication (38, 39), these observations indicate that in a naturalistic setting these medications continue to be in prominent use. Thus, these atypical antipsychotic medications continue to prove necessary and popularly administered despite a need for economic austerity and concerns of financial cutbacks. Further follow-up and illness description remains important in the additional characterization of first-episode schizophrenia illness. Factors to be considered in the future include whether evidence exists for any one of the medication classes (typical vs. atypical), or individual medications within the classes, being more effective than another in long-term management after the initial episode of schizophrenia psychosis (e.g., regarding relapse rates, side-effects, number of hospitalizations, etc.) and whether any neurobiological measure at illness onset can potentially serve as a predictor for better clinical response to any specific medication several years after first presentation or whether any neurobiological measure may predict emergence of side-effects over the long-term course of the illness.

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