Schizophrenia relapse in relation to drug treatment

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ABSTRACT

Objectives: To assess and compare, prospectively, schizophrenia relapse in relation to neuroleptic medication in long term maintenance therapy.

Methods: All schizophrenic patients who met the DSM-IV criteria attending King Khalid University Hospital psychiatry outpatient clinic, Riyadh, Kingdom of Saudi Arabia in January 1994, and who fulfilled the inclusion criteria of the study, were assessed at baseline using the brief psychiatric rating scale (BPRS), quality of life scale and the extrapyramidal rating scale, and at each relapse and 6 weeks after treatment of the relapse and followed for 10 years after being allocated to one of 3 groups of neuroleptic medications depot (group A), conventional (group B) and atypical, clozapine (group C). A data collection form including sociodemographic data and other clinical indices was also completed for the patients.

Results: Seventy-six schizophrenic patients met the DSM-IV diagnostic criteria, but only 59 patients fulfilled the inclusion criteria of the study and 4 patients quit the study. The mean age was 27.45 years and 63.6% were males and 98.2% were Saudis. There was a statistical significance of the BPRS scores before and after relapse for groups A and C, but not for group B. The relapse rates at one year, 2 years, 3 years, and 5 years were in the range 13.3-34.6% for groups A and C but much higher at 35.7-85.7% for group B.

Conclusion: Relapse rate in schizophrenia can be markedly reduced by effective maintenance neuroleptic treatments adhered to by the psychiatrist leaving more room for further reduction of relapse by implementing other measures such as lowering the expressed emotion, psychoeducation and rehabilitation. Further long-term large sample research is needed to affirm this.

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Schizophrenia is the most chronic and disabling of the severe mental disorders with a prevalence of 1% in general populations and a taxing economic burden, mostly from relapse and rehospitalization.[1] Despite highly effective neuroleptic drugs being available, 50% of schizophrenic patients, under normal treatment conditions relapse within one year and frequently spend 15-20% of their time in hospitals.[2] Therefore, the prevention of relapse in schizophrenia remains an enormous public health challenge worldwide, and improvements in this area can have a tremendous impact on morbidity, mortality and quality of life of schizophrenic patients, as well as direct and indirect health care costs.[2-4] However, research on relapse has many difficulties, such as the definition of the concept of relapse, the control of the psychosocial factors affecting relapse, namely: expressed emotions (EE), compliance and psychoeducation, and the adherence to the consensus standards of drug treatments by psychiatrists.[1,5,6] Also, poor premorbid school adaptation and premorbid social withdrawal were found to be associated with earlier relapse.[6-11] Maintenance, neuroleptic medication, was shown to effectively reduce relapse, whereas 25% of patients drop out of treatment after first relapse and

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discontinuation of medication increases relapse 5 times.[1,2,4,12,13] In addition, there is a lack of prospective long-term follow up studies to describe the pattern and nature of relapse and the cultural differences of schizophrenic patients.[7-10]

This prospective study aims at comparing the relapse rate of schizophrenic patients undergoing different drug treatments used at standard regimes over a 10 year period.

Methods. All Schizophrenic patients (n=76) attending the outpatient clinic at King Khalid University Hospital (KKUH), Riyadh, Kingdom of Saudi Arabia in January 1994 were assessed to fulfill the DSM-IV diagnostic criteria and to complete a full history data form. All patients with any comorbidity such as affective symptoms, drug abuse, obsessive compulsive symptoms, any general medical condition, were excluded and therefore, only 59 patients were included in the study. Another 4 patients dropped out over the period of the study. The study group of 55 patients were selected for drug treatment according to their past medication history, response to previous medications and whether first episode or not, for either group A depot medication (only Flupentixol decanoate) or group B a conventional oral neuroleptic (Trifluoperazine, Pimozide, Sulpiride, Flupentixol, and Zuclopenthixol) or a third group C of atypical neuroleptics (clozapine) which was used only for refractory cases. At relapse the plan was to use as much as possible the same medications that the patient was selected for, and only in rare cases and for ethical reasons, other oral conventional antipsychotics would be used temporarily until the patient is stabilized and then discontinued, and the original medication dose will be adjusted according to the needs of the patients. Group B patients on conventional oral neuroleptics were selected to continue the study only if they would be controlled on the same conventional medication. Those who needed different medications were automatically dropped out of the study as shown in the results.

Patients and relatives were informed about the study and verbal consent was obtained. They were given the contacts of the clinic to come for assessment in case they suspected any recurrence of positive symptoms named specifically to the individual patient. All patients were also assessed using the following rating scales at first interview of recruitment in the study and at each relapse detection and at 6 weeks after treatment. a) The Brief Psychiatric Reporting Scale (BPRS), which is a clinician-rated tool to assess change in severity of psychopathology. b) The Quality of Life Scale (QLS), which is measuring directly deficit symptoms in chronic disorders. c) The Extrapyramidal Rating Scale (ESRS), which measures the presence of extrapyramidal side-effects of neuroleptics.[14] Relapse definition in this study was taken as the clear recurrence of the illness positive symptoms that warrant psychiatric drug intervention.[5,6] Also, the accident and emergency (A/E) attendances and the number of hospital admissions were analyzed in comparison to number of assessed relapses. Cases started on clozapine were strictly followed according to the approved safety system for white blood count (WBC), implemented by Novartis company in Saudi Arabia, which is mandatory weekly blood values for 18 weeks and then monthly. The t-test was used to compare rating scales scores at different time scales over the study period.

Results. Seventy-six schizophrenic patients met the DSM-IV diagnostic criteria, but only 59 patients fulfilled the inclusion criteria of the study and 4 patients dropped out for various reasons which left only 55 patients in the study sample. Sociodemographic characteristics of the study sample are shown in **Table 1**. The patients were allocated to the 3 groups as follows: group A = 15

Table 1 - Sociodemographic characteristics of the study sample.

Features	n	(%)
Age (years)	Mean	Range
All	27.45±8.84	(11-70)
Male	27.73±9.35	(11-70)
Female	26.94±7.95	(11-47)
11-20	11	(20)
21-30	30	(54.5)
31-40	11	(20)
41-70	3	(5.5)
Sex		
Male	35	(63.6)
Female	20	(36.4)
Nationality		
Saudi	54	(98.2)
Others	1	(1.8)
Marital status		
Single	34	(61.8)
Married	21	(38.2)
Living status		
With parents	34	(61.8)
With siblings	6	(10.9)
With parents & siblings	5	(9.1)
With other	9	(16.4)
Alone	1	(1.8)
Episodes		
First episode	14	(25.5)
Multi episode	41	(74.5)
Work status		
Unemployed	43	(78.2)
Employed	12	(21.8)
Illness duration (years)	Mean	Range
All	9.7±5.88	(1-24)
Males	9.31±5.76	(1-23)
Females	10.26±6.21	(1-24)

Table 2 - Means scores of BPRS, QLS and ESRS before and after relapses for groups A, B and C.

Group	BPRS mean		P	QLS mean		P	ESRS mean		P
	Before	After		Before	After		Before	After	
A	24±4.8	12.1±3.2	<0.0001	27.4±10.9	28.3±14	0.12	2.1±0.5	1.9±0.8	0.31
B	16±7.4	3.8±4.5	0.18	25.1±9.4	24.2±8.9	0.08	1.7±0.6	1.8±0.3	0.12
C	23.3±5.2	10±2.9	0.05	27.4±13.4	29.3±14.6	0.15	1.16±0.4	1±0.1	0.2

BPRS - Brief Psychiatric Rating Scale, QLS - Quality of Life Scale, ESRS - Extrapyramidal Rating Scale
Test used: t statistical test, P - probability

(27.2%) patients, group B = 14 (25.5%) patients and group C = 26 (47.3%) patients. Group B patients dropped out over time, and only 5 patients (35.7%) completed the study. The mean dosages of depot medication for group A was 38.5±10.90 mg, with a range of 20-60 mg per month, and for group B equivalent to 10.3±5.6 mg of haloperidol daily, and for group C, 283.1±162.9 mgs with a range of 100-750 mg of clozapine daily.

The mean scores of BPRS, QLS and ESRS before and after all relapses for all groups are shown in **Table 2**. The BPRS scores before and after relapse were clearly statistically significant for groups A and C but not for group B, and the QLS scores before and after relapses were not statistically significant for all groups. **Table 3**, shows the rates of relapse for each group at one year, 2 years, 3 years, 5 years and 10 years. This was intended to facilitate comparison with other reports. To assess the validity of relapse assessment, the correlation with the number of admissions and the number of A/E attendances at end of the study period was determined, and it only correlated highly with the number of admissions r = 0.82 and $p<0.0001$.

Table 3 - Relapse rates for all groups.

Groups	One year	2 years	3 years	5 years	10 years
Group A					
N	15	15	15	15	15
n	2	3	4	5	5
RR%	13.3	20	26.7	33.3	33.3
Group B					
N	14	14	10	7	5
n	5	9	8	6	5
RR %	35.7	64.3	80	85.7	100
Group C					
N	26	26	26	26	26
n	4	6	7	8	9
RR%	15.4	23.1	26.9	32	34.6

N - Total number of cases in the group, n - number of relapsing cases, RR% rate of relapse at the time as a percentage

Discussion. As this study aimed at comparing relapse rates in schizophrenic patients who are treated by different neuroleptics chosen according to patient clinical needs, and given the standard recommended dose with assured compliance, patients were not allocated randomly to different medications, as the purpose was not to compare efficiency. Hence, the number of patients was not equal in the groups as the multi episode refractory cases were greater and therefore, group C was double that of group A and B. The finding that only 25.5% of the sample were first episode schizophrenia, and the mean illness duration of the multi episode group is above 9 years, may add negatively to the sample selection and affect response to treatment and therefore, relapse.[6] The preponderance of males in the study sample may be attributed to lack of independence of females to access services or to the social stigma of mental illness being more associated with females in the Saudi culture.[15] However, this male preponderance cannot be explained by the non-participant patients being females as the number was only 4 and cannot account for the difference. The high percentage of Saudi patients is consistent with the regulations of KKUH to accept mostly nationals. The high percentage of unemployed and single patients is consistent with worldwide findings in schizophrenia epidemiology.[1-3] The finding that 98.2% live with families, may have a dual effect where on one hand it may reduce relapse by providing good social support, proper compliance and reliable detection of relapse, however, however, it may increase relapse by high expressed emotion (HEE).[11,16,17]

The average doses used in this study are within the recommended range, but less than other studies for clozapine mean dose, which shows that refractory Saudi schizophrenic patients may need lower doses than in the Western patients. This is difficult to explain, but may be a bias selection of the study sample where milder cases were recruited, or an individual patient response.[9,10,16] The finding that many patients in group B did not complete the

study also shows that first episode patients who respond well to conventional antipsychotics, may have to be transferred to depot medication or atypical neuroleptics soon afterwards to ensure compliance, improvement and to reduce relapse.[12,18] The group C patients were all on clozapine, which indicates their chronicity and resistance to conventional treatments and despite this, the relapse rate of those patients was comparable to group A, which also adds an advantage to clozapine in relapse prevention of refractory schizophrenics over 10 years with minimal extra pyramidal side-effects.[12]

The effect of neuroleptics on BPRS scores was evident in groups A and C comparable to expected rates of score reduction, which reflects marked improvement, but the QLS scores were not statistically significant. The group B high relapse rate results can be understood in view of the large drop out of patients and the conventional neuroleptics low effect on negative symptoms and cognition.[18-20] However, the QLS statistically non-significant results may reflect the low validity of the scale in the Saudi culture where many schizophrenic patients are not expected to work or care for themselves or socialize.[15] The ESRS scores are also conclusive to show that extrapyramidal side-effects were not greater after treatment than before treatment and generally no one group showed more extrapyramidal side-effects than the others. This comparison is acceptable between groups A and C, but for B, the results were only calculated for those who completed the study and many drop outs may have been because of the extrapyramidal side effects. Reviewing those patients who completed the study from Group B, they were found to be on Sulpiride and Pimozide, which are effective on depressive symptoms of schizophrenia and of low extrapyramidal side-effects.[20]

Although the relapse concept definition is controversial, in this study it is unlikely to affect results as the same concept is being used to compare the 3 groups, in addition, the concept used here was consistent with that suggested by many researchers in this area.[5] The relapse rate of one and 2 years is comparable to other reports, but not for the 10-year rate which is higher in this study.[7-10,16,20] However, there was a comparable relapse rate all through for groups A (depot) and C (atypical). This may show that the compliance assured by the depot medication is substituted by the lower side-effects profile and the positive effects on negative symptoms and cognition of atypical neuroleptics.[12,18,20,21] Group B, the conventional antipsychotics, as expected were intolerable over the years and few patients could complete the study probably due to the side-effects profile and their lack of effect and negative symptoms and cognition.[21] Over 3 years, the relapse rate for depot and atypical neuroleptics is less in this sample than in other reports, while it is higher for oral neuroleptics.[7-10,16] This may be explained by the social containment of our patients in the Saudi culture where more than 85% live with families, while 61.8% were single and 76.4% were unemployed.[15] The relapse rate over 10 years is remarkably low in group A and C but not for B. This stresses the point that schizophrenics stabilized on neuroleptics with planned follow up, may continue with a low rate of relapse over many years.[1,7,8,22] This also concords with early studies that repeated relapses worsen the long term prognosis, increase self injury behavior, antisocial behavior and hospital admissions.[2,7,23] The trend of progressive increase of relapse rate in all groups over the years may be explained by other factors which were not controlled for in this study, such as depression, EE, social support, living status, and psychoeducation of patients and families and finally the patient compliance for groups B and C.[6,20,24]

Despite several studies recommending to continue neuroleptics for first episode schizophrenics for 2 years and for multi-episode schizophrenics for 5 years, other studies showed beyond doubt the high rate of relapse after discontinuation of neuroleptics, which stresses the issue supported by this report to maintain drug treatment for a longer number of years to reduce the negative effects of relapse.[1,4,13,22]

The high correlation between the relapse assessment according to the definition used here with the number of admissions for all groups shows that most schizophrenic relapses need hospitalization and the number of admissions reflects to a high validity, the rate of relapse, also, reducing the relapse rate will definitely reduce hospitalization and reduce costs.[2,3,5]

Relapse in schizophrenia is associated with factors related to the illness, the patient, the family life and the psychiatrist compliance with drug treatment recommendations. This study, despite the relatively small number of patients, provides evidence that relapse rates can be effectively decreased by a) ensuring compliance by patient and family support and easy contact with the service, b) adhering to recommended mean dosage of neuroleptics, c) reducing extrapyramidal side-effects by proper selection of neuroleptics, d) early detection of relapse by patient and family and proper intervention, e) long-term maintenance neuroleptic medication, the duration of which should be revised to be much longer than 2 years for first episode and 5 years for multi-episode patients.

All previously outlined factors provide handy and effective measures for clinicians to help their schizophrenic patients by reducing relapse and therefore improving illness outcome and health care efficiency, let alone the implementation of other factors reducing relapse such as psychoeducation

for patients and families, reducing the high EE, and finally, proper rehabilitation programs.[6,25] This study also supports other studies that a) depot neuroleptic medication continues to be effective in reducing relapse rate in schizophrenic patients, b) clozapine reduces relapse rate as effective as depot neuroleptics, c) schizophrenic patients on oral conventional neuroleptics mostly need to be transferred to depot or atypical neuroleptics to ensure low rate of relapse.

Further long-term wide scale prospective studies are necessary to accomplish the specific clinical dimensions of schizophrenia relapse in relation to neuroleptic medications.

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References

1. Kissling W editor. Guidelines for neuroleptic relapse prevention in Schizophrenia. Berlin: Springer-Verlag; 1991.
2. Kissling W. Compliance, quality assurance and standards for relapse prevention in Schizophrenia. ***Acta Psychiatr Scand*** 1994; 89 (Suppl 382) 16-24.
3. Johnstone EC, Geddes J. How high is the relapse rate in Schizophrenia? ***Acta Psychiatr Scand*** 1994; 89 (Suppl 382): 6-10.
4. Glick ID, Berg PH. Time to study discontinuation, relapse, and compliance with atypical or conventional antipsychotics in Schizophrenia and related disorders. ***Int Clin Psychopharmacol*** 2002; 17: 65-68.
5. Falloon IRH, Marshall GN, Boyd JL, Razani J, Wood-Siverio C. Relapse in schizophrenia: a review of the concept and its definitions. ***Psychol Med*** 1983; 13: 469-477.
6. Ayuso-Gutierrez JL, del-Rio-Vega JM. Factors influencing relapse in the long-term course of schizophrenia. ***Schizophr Res*** 1997; 28: 199-206.
7. Ohmori T, Ito K, Abekawa T, Koyama T. Psychotic relapse and maintenance therapy in paranoid Schizophrenia: a 15 year follow up. ***Eur Arch Psychiatry Clin Neurosci*** 1999; 249: 73-78.
8. Eaton WW, Thara R, Federmann E, Tien A. Remession and relapse in Schizophrenia: the Madras longituidinal study. J ***Nerv Ment Dis*** 1998; 186: 357-363.
9. Tsoi WF, Kok LP, Chew SK. A five-year follow-up study of Schizophrenia in Singapore. ***Singapore Med J*** 1985; 26: 171-177.
10. Chowdhury AN, Mukhergee A, Ghosh K, Chowdhury S, Das Sen K. Horizon of a new hope: Recovery of Schizophrenia in India. ***International Medical Journal*** 1999; 6: 181-185.
11. Mari JDJ, Streiner DL. An overview of family interventions and relapse on Schizophrenia: meta-analysis of research findings. ***Psychol Med*** 1994; 24: 565-578.
12. Csernansky-John G, Schuchart-Emily K. Relapse and rehospitalization rates in patients with Schizophrenia: effects of second generation antipsychotics. ***CNS Drugs*** 2002; 16: 473-484.
13. Linden M, Godemann F, Gaebel W, Kopke W, Muller P, Muller-Spahn F, et al. A prospective study of factors influencing adherence to a continuous neuroleptic treatment programs in schizophrenia patients during 2 years. ***Schizophr Bull*** 2001; 27: 585-596.
14. Task Force Committee, American Psychiatric Association. Handbook of Psychiatric Measures. 1st ed. Washington (DC): The American Psychiatric Association; 2000.
15. Al-Subaie A, Alhamad A. Psychiatry in Saudi Arabia. In: Al-Issa I, editor. Mental Illness in the Islamic World. Madison (CN): International Universities Press, INC; 2000.
16. Razali MS, Yahya H. Compliance with treatment in Schizophrenia: a drug intervention programme in a developing country. ***Acta Psychiatr Scand*** 1995; 91: 331-335.
17. Pitschel-Walz G, Leucht S, Bauml J, Kissling W, Engel RR. The effect of family interventions on relapse and rehospitalization in Schizophrenia. a meta-analysis. ***Schizophr Bull*** 2001; 27: 73-92.
18. Kinon BJ. The routine use of atypical antipsychotic agents: maintenance treatment. ***J Clin Psychol*** 1998; 59 (Suppl 19): 18-22.
19. Marland GR, Cash K. Long-term illness and patterns of medicine taking: are people with Schizophrenia a unique group? ***J Psychiatr Ment Health Nurs*** 2001; 8: 197-204.
20. Mauri MC, Bitetto A, Fabiano L, Laini V, Steinhilber C, Forrier M et al. Depressive symptoms and Schizophrenia relapses: the effect of four neuroleptic drugs. ***Prog Neuropsychopharmacol Biol Psychiatry*** 1999; 23: 43-54.
21. Hogarty GE, Ulrich RF. The limitations of antipsychotic medication on Schizophrenia relapse and adjustment and the contributions of psychosocial treatment. ***J Psychiatry Res*** 1998; 324: 243-250.
22. Kane JM, Aguglia E, Altamura AC, Ayuso-Gutierrez JL, Bruneela N, Fleischhlacker WW, et al. Guidelines for depot antipsythotic treatment in Schizophrenia. European neuropsychopharmacology consensus conference in Siena, Italy. ***European Neuropharmacology*** 1998; 8: 55-66.
23. Kennedy MG, Schepp KG, O'Connor FW. Symptom self-management and relapse in Schizophrenia. ***Arch Psychiatr Nurs*** 2000; 14: 266-275.
24. Johnson DAW. The significance of depression in the prediction of relapse in chronic schizophrenia. ***Br J Psychiatry*** 1988; 152: 320-323.
25. Jegensen P. Early signs of psychotic relapse in Schizophrenia. ***Br J Psychiatry*** 1998; 172: 327-330.