

Factors associated with relapse in schizophrenia

N J B Kazadi, MD

M Y H Moosa, MMed (Psych), FCPsych, MCFP

F Y Jeenah, MMed (Psych)

Division of Psychiatry, University of the Witwatersrand, Johannesburg

Aim. Early identification and prevention of relapse in patients with schizophrenia has significant therapeutic and socio-economic implications. The aim of this study was to determine the factors, if any, that may be associated with relapse in a group of patients in Johannesburg.

Method. Patients were recruited from mental health outpatient clinics in a predominantly residential area during the period January 1995 - June 2005. They were included if a review of their records confirmed a diagnosis of schizophrenia according to the *Diagnostic and Statistical Manual of Mental Disorders* (4th edition) (DSM-IV); they had no other psychotic illness; and they were ≥ 18 years old. Patients were excluded if the diagnosis of schizophrenia had first been made in the preceding 6 months. Demographic and clinical characteristics of the patients were obtained from their case notes.

Results. Of the 217 patients who were included in the study, 61.8% ($N=134$) had a history of at least 1 relapse. There was no significant difference ($p>0.05$) between those who relapsed and those who did not relapse in terms of gender, marital status or employment status. Approximately 46% ($N=61$) of those who relapsed had co-morbid psychiatric disorders, compared with 10.8% ($N=9$) in those who did not relapse ($p<0.0001$), but there was no significant difference between the two groups when comparing the presence of co-morbid medical disorder ($p=0.348$). Nearly half ($N=63$) of patients who relapsed had a history of substance abuse ($p=0.0054$); cannabis was significantly more abused ($p=0.0014$). Two-thirds ($N=138$) of the study population did not adhere to their treatment, of whom 80.4% ($N=107$) experienced a relapse ($p<0.0001$). Significant multiple logistic regression models for patients who relapsed included poor adherence due to side-effects (odds ratio (OR)=3.032; $p=0.023$; 95% confidence interval (CI) 1.168 - 7.870); poor adherence due to lack of insight (OR=5.29; $p<0.0001$; 95% CI 2.28 - 12.20), and co-morbid depressed mood (OR=5.33; $p<0.001$; 95% CI 2.32 - 12.22).

Conclusion. Co-morbid depressed mood, poor adherence owing to lack of insight, and medication side-effects were the factors most likely to increase the risk of relapse in patients with schizophrenia. Risk of relapse may be reduced when the treating psychiatrist identifies and addresses these factors.

Schizophrenia is a chronic and disabling illness that affects approximately 1% of the world's population. It is often accompanied by relapse even while on treatment.¹ Relapse rates vary from 50% to 92%² and are similar in developed and developing countries, despite the former having well-established mental health services. Among South Africans, there are few published data regarding the prevalence and factors associated with relapses; this study was intended to address that need.

Relapse in schizophrenia is broadly recognised as the re-emergence or the worsening of psychotic symptoms. More specifically, certain criteria are used to define relapse; they include aggravation of positive or negative symptoms, hospital admission in the past 6 months, and more intensive case management and/or a change in medication.³ Relapse may result in hospitalisation, treatment resistance, cognitive impairment owing to progressive structural brain damage, personal distress, incarceration, and interference with rehabilitation efforts.⁴ Relapse increases the economic burden on health care systems because of its associated morbidity and re-admissions to hospital. Prevention of relapses could have significant therapeutic and socio-economic implications.^{3,5} Internationally, the factors commonly associated with relapse include poor adherence to treatment, substance abuse, co-morbid psychiatric illness, a co-morbid medical and/or surgical condition, stressful life events, and the treatment setting.^{6,7}

The medication compliance rate for non-psychiatric illnesses is 76%, while that for psychiatric illnesses is 58%.⁸ More specifically, about half of the patients with schizophrenia are non-adherent to treatment.^{9,10} This non-adherence may be due to factors that are patient-related (e.g. substance abuse, forgetfulness, anxiety about side-effects, inadequate knowledge, lack of insight, lack of motivation, fear of stigma); health care-related (e.g. poor patient/health care provider relationship, poor services and access to services, poor staff training);¹¹ socio-economically-related (e.g. illiteracy, low level of education)¹² or treatment-related (e.g.

poly-pharmacology, complex treatment regimens).^{13,14} Among South Africans, cultural and social attitudes and belief systems are speculated as common reasons for poor adherence to treatment.¹⁵

Substance abuse is common among patients with schizophrenia¹⁶ and can lead to relapse independent of its effects on treatment adherence. The lifetime prevalence is estimated to be as high as 47%,¹⁷ with approximately 33% of patients having an alcohol dependence disorder.¹⁸ Commonly abused substances include nicotine, alcohol, cannabis and cocaine. In South African studies, alcohol abuse and cannabis abuse were reported as significant factors that contributed to relapse in all mental illnesses,¹⁹ and cannabis, methaqualone and alcohol abuse as having contributed to relapse in acute psychotic states.²⁰

Stressful life events are often associated with the onset of a psychotic relapse, usually in the 3 weeks prior to the relapse.²¹⁻²³ Life stressors may be both internal (e.g. thoughts and feelings) and external (e.g. death of a close relative).²⁴ Other stressors include chronic interpersonal stress, poverty, homelessness, criminal victimisation and stigma. Patients with schizophrenia are more sensitive and more susceptible to the negative effects of even minor stressors. Unemployment and the loss of a close family member are reported as significant causes of relapse in South Africa.²⁵

Depression in schizophrenia has been associated with higher rates of relapse, poor outcome, impaired functioning, personal suffering and even suicide.^{26,27} Approximately 18 - 55% of patients with schizophrenia make at least 1 suicide attempt, while 10 - 13% of patients succeed in committing suicide.⁷

The aim of this study was to determine the factors, if any, among patients with schizophrenia that may be associated with relapses. The specific objectives were to compare the demographic and clinical characteristics of a group of patients with schizophrenia who relapsed, with those who did not relapse.

Method

Study sample

The researchers approached the psychiatric nursing staff of mental health outpatient clinics in Johannesburg for a list of possible patients with a diagnosis of schizophrenia. Patients from this list were then randomly selected using the card-shuffling technique. Patients were included in the study if a review of their records confirmed a diagnosis of schizophrenia according to DSM

IV criteria⁷ and they had no other psychosis, were ≥ 18 years old, and had attended the clinics between the period January 1995 and June 2005. Patients were excluded if the diagnosis of schizophrenia had first been made in the preceding 6 months, to avoid any bias in detecting relapses in these patients. The University of the Witwatersrand's Human Research Ethics Committee (HREC) approved the study.

Relapse and adherence criteria

Relapse was identified in the cases of patients who had documented evidence of either re-emergence or aggravation of psychotic symptoms, a consultation with a psychiatrist and medication change for deterioration of illness, and/or admission to a psychiatric unit in a hospital in accordance with the Mental Health Care Act.³ Planned hospital admission for a non-related illness or for special investigations was not deemed to be a relapse.

Adherence to treatment was considered to be poor if there was failure to fill any prescription, refusal to take medication, stopping treatment prematurely, and reports of taking medication at the wrong time and/or incorrect dosage.

Demographic and clinical characteristics of the patients (gender, age, marital status, source of income, highest level of education, substance abuse, presence and type of co-morbid psychiatric illness, presence of co-morbid medical/surgical illness, stressful life events, presence of and type of stressor, insight) that affect adherence were obtained directly from their case notes.

Statistical analysis

Descriptive statistics were computed as mean and frequencies (count and percentages). The two-tailed paired *t*-test was used to compare continuous characteristics (age) between the groups. Comparisons between relapse and non-relapse groups (outcome variable) with respect to patient characteristics (age, gender, highest level of education, employment status, poor adherence, substance abuse, co-morbid medical/surgical illness, co-morbid psychiatric illness and psychosocial stressors) were examined by the use of contingency tables (chi-squared test with Yates correction and Fisher's exact test, ORs). The variables showing significant association ($p < 0.05$) in the bivariate analyses were entered into the survey logistic regression to obtain the adjusted ORs. The criterion for removal in the multiple logistic regression analysis was $p > 0.05$. All analyses were calculated by the Statistical Package for Social Sciences 10.0 for Windows (SPSS Inc., Chicago, USA).

Results

Demographic characteristics

A total of 217 patients with a diagnosis of schizophrenia were included in the study. Most (61.8%, 134) of the study population were patients who relapsed, i.e. had a history of at least 1 relapse. The mean age of patients who relapsed was 42.5 years (standard deviation (SD)=10.5; 95% CI 40.7 - 44.3; min. 21 years, max. 75 years) while that for patients who did not relapse was 49.3 years (SD=13.7; 95% CI 46.3 - 52.3; min. 21 years, max. 83 years).

About 30.6% (41) of patients who relapsed had achieved a primary level of education, and 48.5% (65) a secondary level of education. By comparison, 15.7% (13) of the patients who did not relapse had achieved a primary level of education, and 72.3% (60) a secondary level of education (Fisher's exact=0.006; $p=0.01$) (Table I). There was no significant difference between the two groups regarding gender (Fisher's exact=1.000, $p=0.98$); marital status (Fisher's exact=0.001, $p=0.12$); receiving state grants (Fisher's exact=0.471, $p=0.52$); receiving family support (Fisher's exact=0.203, $p=0.31$); and employment status (Fisher's exact=0.203, $p=0.31$).

Clinical characteristics

Approximately 46% (61) of patients who relapsed had co-morbid psychiatric disorders (40.2% had a depressed mood) compared with 10.8% (9) of patients who had not relapsed ($p<0.0001$) (Table II). Further, 15.2% (20) of patients who relapsed had either attempted suicide or had suicidal ideation compared with none among those who had not relapsed ($p=0.0002$). There was no significant difference between the two groups regarding co-morbid medical disorders (Fisher's exact=0.286, $p=0.35$).

Nearly 50% (63) of the patients who relapsed had a history of substance use/abuse compared with 30.1% (25) of patients who had not relapsed ($p<0.05$); cannabis was the preferred drug of use/abuse ($p<0.0001$).

Two-thirds (138) of the study population were not fully adherent to their treatment, of whom 80.4% (107) had experienced a relapse (Fisher's exact=0.000, $p<0.0001$). The factors that were significantly associated with poor adherence included lack of insight (Fisher's exact = 0.000, $p<0.0001$) and adverse medication effects (Fisher's exact=0.000, $p=0.0003$) (Fig. 1). Poor relationships with a health care provider (Fisher's exact=1.00, $p=0.80$) or living great distances from the clinic (Fisher's exact=0.14, $p=0.09$) did not appear to be associated with relapses.

Table I. Demographic characteristics of the study population

Variables	Relapse N=134 (100%)	Non-relapse N=83 (100%)	
Gender*			
Males	93 (69.4)	56 (69.1)	
Females	41 (30.6)	25 (30.8)	Fisher's exact=1.000; $p=0.98$
Marital status*			
Single	96 (73.3)	49 (59.0)	
Married	18 (13.7)	20 (24.1)	
Divorced	16 (12.2)	13 (15.7)	
Unknown	1 (0.8)	1 (1.2)	Fisher's exact=0.001; $p=0.12$
Education			
No formal	19 (14.2)	8 (9.6)	
Primary	41 (30.6)	13 (15.7)	
Secondary	65 (48.5)	60 (72.3)	
Tertiary	9 (6.7)	2 (2.4)	Fisher's exact=0.006; $p=0.01$
Source of income[†]			
Nil	4 (3.0)	4 (4.8)	
Employed	9 (6.7)	9 (10.8)	Fisher's exact=0.203; $p=0.31$
State grants	112 (83.6)	66 (79.5)	Fisher's exact=0.471; $p=0.52$
Family support	61 (45.5)	30 (36.1)	Fisher's exact=0.203; $p=0.31$

*Totals do not add up to 100%.

[†] Respondents in each category who reported 'yes' to having a certain source of income.

Although stressful life events were not significantly associated with relapses (Fisher's exact=0.000, $p=0.001$), patients with relapses had more frequent relationship difficulties (Fisher's exact=0.08, $p=0.006$) and personal stressors (Fisher's exact=0.018, $p=0.02$) compared with patients who had not relapsed (Fig. 2).

Multiple logistic regression models were applied to identify factors that best predicted whether or not a patient could relapse. Significant models for patients included partial adherence due to side-effects (OR=3.032, $p<0.05$, 95% CI 1.168 - 7.870); partial adherence owing to impaired insight (OR=5.278, $p<0.0001$, 95% CI 2.284 - 12.198); and co-morbid depressed mood (OR=5.328, $p<0.001$, 95% CI 2.323 - 12.219).

Discussion

Relapse rates

The most common outcome of schizophrenia is usually a remitting course with one or multiple relapses in 50 - 92% of cases.² Patients on medication have a relapse rate of 40%, while those who discontinue their treatment have a 1-year relapse rate of 65% and a 2-year rate of >80%.²⁸ The patients in this study showed similar high rates of relapse. About two-thirds of the patients had at least 1 relapse, with the majority having ≥ 2 relapses.

In the management of schizophrenia, psychosocial approaches in addition to antipsychotic drug therapy may result in a significant reduction of relapses compared with using antipsychotic treatment only.²⁸ The psychosocial approaches include community programmes (case management, assertive community treatment, foster home care, day treatment centres and psychosocial rehabilitation centres) and individual or family psychotherapeutic approaches (social skills training, personal therapy and psycho-education). South Africa has very little – if any – in the way of

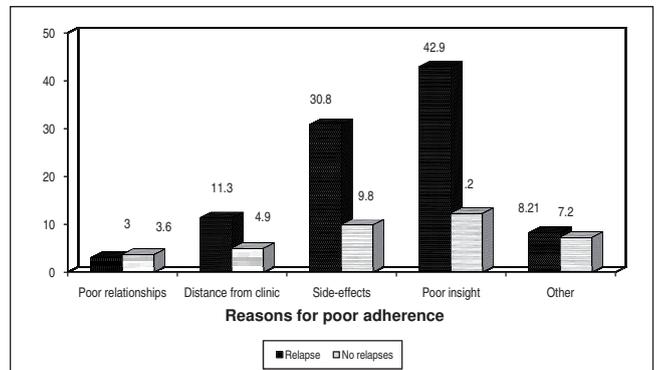


Fig. 1. Reasons for poor adherence in the study population.

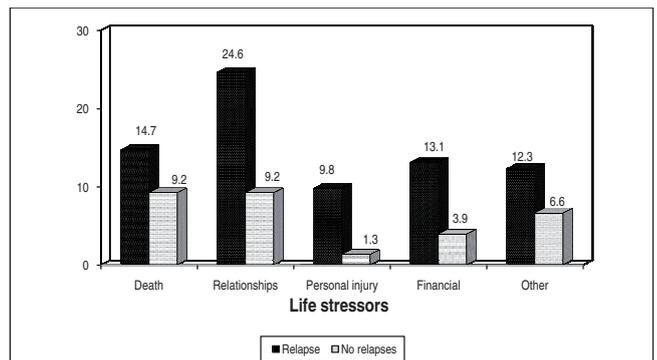


Fig. 2. Life stressors in the study population.

such services available. Patients with schizophrenia are usually discharged from hospitals to follow-up at their nearest community mental health clinics, which focus mainly on pharmacotherapy, with little psychosocial support services owing to a lack of human and material resources²⁹ and the difficulties of integrating various treatment modalities in community-based outreach teams – even where the appropriate range of services is available.³⁰ Despite these constraints, relapse rates are similar to those of developed countries, notwithstanding the other benefits and qualities that are brought about by psychosocial approaches.

Table II. Clinical characteristics of the study population

Variables	Relapse N=134 (100%)	Non-relapse N=83 (100%)	
Co-morbid psychiatric disorder	61 (45.5)	9 (10.8)	Fisher's exact=0.000; $p<0.05$
Personality disorder	3 (2.3)	2 (2.5)	Fisher's exact=1.00; $p=0.89$
Depressed mood	53 (40.2)	6 (7.6)	Fisher's exact=0.000; $p<0.05$
Suicidal ideation	20 (15.2)	0 (0.0)	Fisher's exact=0.0; $p<0.05$
Other	1 (0.8)	0 (0.0)	
Co-morbid medical disorder	43 (32.1)	21 (25.3)	Fisher's exact=0.286; $p=0.35$
Substance use/abuse	63 (47.4)	25 (30.1)	Fisher's exact=0.000; $p=0.03$
Poor adherence	107 (80.4)	31 (37.8)	Fisher's exact=0.000; $p<0.05$
Life stressors	72 (59.0)	18 (23.6)	Fisher's exact=0.00; $p=0.001$

Factors associated with relapses

Partial adherence

In mentally ill patients, partial adherence to treatment remains a therapeutic challenge and a factor that is difficult to quantify; it is compounded by the fact that adherence rates vary for different psychotropic medications: 58% for antipsychotics and 65% for antidepressants.³¹ We observed an overall adherence rate of 64.2%, which concurs with other reported adherence rates.³²⁻³⁵ However, this finding must be qualified in that self-reports of adherence are not always reliable.³¹ For example, patients might not have revealed the extent of their non-adherence for fear of disappointing the clinician. Nevertheless, other methods of assessing adherence (measurement of medication in the blood or urine, clinician rating of response to treatment, pill count, caregiver reports, presence of medication side-effects) also have limitations regarding reliability. It is important to note, furthermore, that poor adherence is not always significantly associated with relapses.²

The factors associated with poor adherence to treatment in the diagnostic group under review were medication side-effects and lack of insight. Poor insight contributed to a 5.2-times increase in the risk of relapse – a finding that is consistent with other studies.¹² However, other researchers argue that the relationship between insight and adherence is not always straightforward and may be without a direct relationship;³⁶ e.g. it is possible that the lack of insight in this population might be related to a lower level of formal education and a lack of understanding of mental illness and its phenomena.

Patients who default on their treatment have said that treatment side-effects^{14,37} together with complex treatment regimens³⁸ are the main reasons for their poor adherence. The majority of our patients were on typical antipsychotic medication and reported side-effects (mostly extra-pyramidal effects and impotence) as contributing to their poor adherence, which is similar to other reported findings.³⁹ However, this association between medication side-effects and adherence is not generally clearly established^{40,41} because many patients adhere to their medication despite treatment side-effects,¹² and a history of side-effects is not always predictive of future non-adherence.³⁶ Further, recent studies report no added benefits of the atypicals in terms of efficacy, discontinuation rates, adverse effects or quality of life, compared with the typical antipsychotics.^{32,33,42-45}

Depressed mood

A quarter of all patients developed a depressed mood during the period studied, increasing the risk of a relapse by 5.3 times.

Other studies on depression associated with schizophrenia show a variation ranging from a high of 75% to a low of 7%.^{26,46} Depression symptoms may appear at any time during the course of schizophrenia and contribute to relapse and a decrease in quality of life.^{47,48} However, this is contradicted by Robinson *et al.*⁴⁹ who reported that despite a possible relationship between mood symptoms and relapse, neither the severity of baseline depressive symptoms nor the presence of mood symptoms was related to relapse and had no prognostic value. Despite these contradictory findings, early detection and management of depression symptoms may decrease the risk of psychotic relapse and it is therefore important that mental health practitioners should identify depressive moods and separate them from the deficit (negative) features of schizophrenia.

Substance abuse

Although substance abuse was very common among our study population, there was no significant association with relapses. This finding differs from previous findings of strong associations with relapses⁵⁰⁻⁵² and a greater risk of re-hospitalisation.⁵³ Substance abuse may exacerbate psychotic symptoms, and abused drugs may also lead to transient symptom reduction.⁵⁴ However, some studies report no association between substance abuse and relapse.⁵⁵ It must be emphasised nevertheless that although it is not clear that substance abuse in patients with schizophrenia results in relapse, it does lead to *inter alia* increased psychosocial problems, infections, sexually risky behaviour, and hostile and disorganised behaviour – and more so in the presence of other health-related problems, poverty, insufficient food, poor housing and widespread unemployment.

Co-morbid medical illnesses

Surprisingly, only a third of the patients with relapses had co-morbid medical illnesses, despite published reports that co-morbid medical disorders exacerbate the relapse process.^{56,57} In South Africa, mental health services remain marginalised and poorly integrated with general medical services in the primary health care system.^{29,49} Co-morbid medical illnesses are managed by different services, and it is possible that adequate attention is not paid to recording these co-morbid medical disorders in case notes at mental health clinics.

Age, education, life stressors and patient-provider relationships

Other reported factors associated with relapse include age,^{49,58} education,² life stressors and patient-provider relationships. These and other studies^{2,3} failed, however, to confirm these

associations. The relapses tended to occur in the age group <50 years and, although this variable lacked a statistically predictive power of relapse, there was a trend towards younger patients being more likely to relapse. Relapsing patients in this study population were more likely to have achieved only a primary level of education. Schizophrenia tends to have an early age of onset and a chronic course with relapses and a declining level of functioning that contributes to early school drop-out. It is difficult to elucidate a causal relationship between life events and relapse in a retrospective study. The lack of any association between patient-provider relationship and non-adherence should be viewed in the working context; in our setting, doctors change every 6 months. Chronic schizophrenic patients, furthermore, could be compromised by their illness and unable to establish a committed therapeutic alliance with their psychiatrists.

Limitations

Other reported factors associated with relapses (such as pre-morbid level of functioning, expressed emotion and duration of untreated psychosis) were not considered in this study and would be better obtained via other study designs. Moreover, the small sample size might have limited our ability to detect statistically meaningful differences.

In any retrospective study design, some data might not have been recorded in case notes, and patients might have been erroneously included or excluded. The design also raises the question of patients' ability to recall events over several weeks between clinic visits, which is compounded by the fact that patients with schizophrenia suffer from some cognitive impairment. However, the majority of our patients' records contained all the data required, and the conclusions drawn are therefore reliable. The study is generalisable, insofar as our study population experiences socio-politico-economic factors and resources that are similar to those experienced by average South African patients with schizophrenia.

Conclusions

Despite recent therapeutic progress, relapse in schizophrenia is a common and major problem among South Africans. The presence of a co-morbid depressed mood, poor adherence due to a lack of patient insight, and medication side-effects appear to be the factors most likely to increase the risk of a relapse. It is important that, in a local context, the treating psychiatrist identifies and treats mood features along with establishing ways of improving insight and adherence to treatment. If atypical antipsychotic treatments (versus typical antipsychotics) can improve adherence

rates, significant reductions in relapse rates and service costs could result.

References

- Gelder MG, Lopez-Ibor JJ, Andreasen NC. *New Oxford Textbook of Psychiatry*. Oxford: Oxford University Press, 2000: 567-621.
- Suzuki Y, Yasumura S, Fukao S, et al. Associated factors of rehospitalization among schizophrenic patients. *Psychiatry Clin Neurosci* 2003; 57: 555-561.
- Almond S, Knapp M, Francois C, et al. Relapse in schizophrenia: costs, clinical outcomes and quality of life. *Br J Psychiatry* 2004; 184: 346-351.
- Piggot TA, Carson WH, Saha AR, et al. Aripiprazole for the prevention of relapse in stabilized patients with chronic schizophrenia: a placebo-controlled 26-week study. *J Clin Psychiatry* 2003; 64: 1048-1057.
- Knapp M, King D, Pugner K, Lapuerta P. Non-adherence to antipsychotic medication regimens: associations with resource use and costs. *Br J Psychiatry* 2004; 184: 509-516.
- Harris MG, Henry LP, Harrigan SM, et al. The relationship between duration of untreated psychosis and outcome: an eight-year prospective study. *Schizophr Res* 2005; 79: 85-93.
- Diagnostic and Statistical Manual of Mental Disorders – DSM-IV-TR*. 4th ed. Washington DC: American Psychiatric Association, 2002.
- Awad GA. Antipsychotic medications: compliance and attitudes towards treatment. *Curr Opin Psychiatry* 2004; 17: 75-80.
- Hudson TJ, Owen RR, Trush CR, et al. A pilot study of barriers to medication adherence in schizophrenia. *J Clin Psychiatry* 2004; 65: 211-216.
- Valenstein M, Blow FC, Copeland LA, et al. Poor antipsychotic adherence among patients with schizophrenia: medication and patient factors. *Schizophr Bull* 2004; 30: 255-264.
- Lacro JP, Dunn LB, Dolder CR, et al. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. *J Clin Psychiatry* 2002; 63: 892-908.
- Fenton WS, Blyler CR, Heinssen RK. Determinants of medication adherence in schizophrenia: Empirical and clinical findings. *Schizophr Bull* 1997; 4: 637-651.
- Suzuki T, Uchida H, Takeuchi H, et al. Simplifying psychotropic medication regimen into a single night dosage and reducing the dose for patients with chronic schizophrenia. *Psychopharmacology* 2005; 181: 566-575.
- Perkins DO. Predictors of nonadherence in patients with schizophrenia. *J Clin Psychiatry* 2002; 63: 12-16.
- Gillis LS, Koch A, Joyi M. Improving compliance in Xhosa psychiatric patients. *S Afr Med J* 1989; 76: 205-208.
- Swofford CD, Kasckow JW, Scheller-Gilkey G, et al. Substance use: a powerful predictor of relapse in schizophrenia. *Schizophr Res* 1996; 20: 145-151.
- Regier DA, Farmer ME, Rae DS. Comorbidity of mental disorders with alcohol and other drug abuses. *JAMA* 1990; 264: 2511-2518.
- Salloum IM, Moss HB, Daley DC. Substance abuse and schizophrenia: impediments to optimal care. *Am J Drug Alcohol Abuse* 1991; 17: 321-336.
- Solombela PW, Uys LR. Factors influencing the relapse of outpatients with schizophrenia in the Kentani area of Transkei. *Curationis* 1994; 17: 24-28.
- Gillis LS, Sandler R, Jakoet A, Elk R. Readmissions to a psychiatric hospital: Outcome on follow-up. *S Afr Med J* 1986; 70: 735-739.
- Pourmand DD, Kavanagh DJ, Vaughan K. Expressed emotion as predictor of relapse in patients with comorbid psychoses and substance use disorder. *Aust N Z J Psychiatry* 2005; 39: 473-478.
- Compton MT, Weiss PS, West JC, et al. The associations between substance use disorders, schizophrenia-spectrum disorders, and Axis IV psychosocial problems. *Soc Psychiatry Psychiatr Epidemiol* 2005; 40: 939-946.
- Murray RM, Castle DJ. Genetic and environmental risk factors for schizophrenia. In: Gelder MG, ed. *Oxford Textbook of Psychiatry*. Oxford: Oxford University Press, 2000.
- Hunter PE, Storat B. Psychosocial triggers of relapse in persons with chronic mental illness: A pilot study. *Ment Health Nurs* 1994; 15: 67-72.
- Mwaba K, Molamu RB. Perceived causes of relapse among a sample of recovering patients at a Mafikeng Hospital. *Curationis* 1998; 21: 55-57.
- Siris SG. Depression in schizophrenia: Perspective in the era of "atypical" antipsychotic agents. *Am J Psychiatry* 2000; 157: 1379-1389.
- Tollefson GD, Sanger TM, Lu Y, et al. Depressive signs and symptoms in schizophrenia: A prospective blinded trial of olanzapine and haloperidol. *Arch Gen Psychiatry* 1998; 55: 250-258.
- Hogarty GE, Ulrich RF. The limitations of anti-psychotic medication on schizophrenia relapse and adjustment and the contributions of psychosocial treatment. *J Psych Res* 1998; 32: 243-250.
- Joubert PM. Community psychiatry in South Africa. *SA Psych Rev* 2002; 5: 4-6.
- Carpenter WT. Maintenance therapy of persons with schizophrenia. *J Clin Psychiatry* 1996; 57: 10-16.

31. Marder SR. Overview of partial adherence. *J Clin Psychiatry* 2003; 64: 3-9.
32. Jones PB, Barnes TRE, Davies L, et al. Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia. *Arch Gen Psychiatry* 2006; 63: 1079-1087.
33. Rosenheck RA. Outcomes, costs, and policy caution: A commentary on the cost utility of the latest antipsychotic drugs in schizophrenia study. *Arch Gen Psychiatry* 2006; 63: 1074-1076.
34. Lieberman JA, Scott Stroup T, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *New Engl J Med* 2005; 353: 1209-1223.
35. Thieda P, Beard S, Richter A, Kane J. An economic review of adherence with medication therapy in the treatment of schizophrenia. *Psychiatr Serv* 2003; 54: 508-516.
36. Olsson M, Mechanic D, Hansell S, et al. Predicting medication non adherence after hospital discharge among patients with schizophrenia. *Psychiatr Serv* 2000; 51: 215-222.
37. Burton SC. Strategies for improving adherence to second-generation antipsychotics in patients with schizophrenia by increasing ease of use. *J Psych Pract* 2005; 11: 369-378.
38. Razaly MS, Yahya H. Adherence with treatment in schizophrenia. A drug intervention program in a developing program. *Acta Psychiatr Scandinav* 1995; 91: 331-335.
39. Leucht S, Barnes TRE, Kissling W, et al. Relapse prevention in schizophrenia with new-generation antipsychotics: A systematic review and exploratory meta-analysis of randomized, controlled trials. *Am J Psychiatry* 2003; 160: 1209-1222.
40. Schooler NR. Relapse and rehospitalization: comparing oral and depot antipsychotics. *J Clin Psychiatry* 2003; 64: 14-17.
41. Fleishhacker WW, Melse U, Gunther V, et al. Adherence with antipsychotic drug treatment: influence of side-effects. *Acta Psychiatr Scand* 1994; 89: 11-21.
42. Lieberman JA, Stroup TS, McEvoy JP, et al. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigation. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005; 353: 1209-1223.
43. Lieberman JA. Comparative effectiveness of antipsychotic drugs: A Commentary on Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1) and Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). *Arch Gen Psychiatry* 2006; 63: 1069-1072.
44. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. *Arch Gen Psychiatry* 2003; 60: 553-564.
45. Chakos M, Lieberman J, Hoffman E, et al. Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials. *Am J Psychiatry* 2001; 158: 518-526.
46. Du Preez RR, Griffith WC, Page M. Major depressive disorder as a co-morbid diagnosis in schizophrenia versus the diagnosis of schizoaffective disorder – depressed type. *S Afr Psychiatry Rev* 2005; 8: 134-139.
47. Elbogen EB, Swanson JW, Swartz MS, et al. Medication nonadherence and substance abuse in psychotic disorders: impact of depressive symptoms and social stability. *J Nerv Ment Dis* 2005; 193: 673-679.
48. Birchwood M, Mason R, Macmillan F, et al. Depression, demoralization and control over psychotic illness: a comparison of depressed and non-depressed patients with a chronic psychosis. *Psychol Med* 1993; 23: 387-395.
49. Robinson D, Woerner MG, Ma J, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Arch Gen Psychiatry* 1999; 56: 241-247.
50. Margolese HC, Carlos Negrete J, Tempier R, et al. A 12-month prospective follow-up study of patients with schizophrenia-spectrum disorders and substance abuse: changes in psychiatric symptoms and substance use. *Schizophr Res* 2006; 83: 65-75.
51. de Leon J, Diaz FJ. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophr Res* 2005; 76: 135-157.
52. de Leon J. Atypical antipsychotic dosing: the effect of smoking and caffeine. *Psychiatr Serv* 2004; 55: 491-493.
53. Sullivan G, Wells KB, Morgenstern H, Leake B. Identifying modifiable risk factors for rehospitalization: A case control study of seriously mentally ill persons in Mississippi. *Am J Psychiatry* 1995; 152: 1749-1752.
54. Dixon L, Haas G, Weiden P, et al. Acute effects of drug abuse in schizophrenic patients: clinical observations and patients self-reports. *Schizophr Bull* 1990; 16: 69-79.
55. Warner R, Taylor D, Wright J, et al. Substance use among the mentally ill: prevalence, reasons for use, and effects on illness. *Am J Orthopsychiatry* 1994; 64: 30-39.
56. Fenton WS. Comorbid conditions in schizophrenia. *Curr Opin Psychiatry* 2001; 14: 17-23.
57. Green AI, Canuso CM, Brenner MJ, Wojcik JD. Detection and management of comorbidity in patients with schizophrenia. *Psychiatr Clin N Am* 2003; 26: 115-139.
58. Dolder C, Lacro J, Jeste DV. Adherence to antipsychotic and nonpsychiatric medications in middle-aged and older patients with psychotic disorders. *Psychosom Med* 2003; 65: 156-162.