Early Medication Adherence and Insight Change in First-Episode Psychosis

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Abstract

Objective: Adherence to treatment is a determining factor for symptomatic remission and relapse prevention following a first episode of psychosis (FEP). Risk factors for poor adherence have consistently involved a lack of insight. While insight can improve considerably during the first months of treatment, little is known about the relation between early change in insight and medication adherence. **Method:** Eighty-eight FEP participants were rated on insight and positive, negative, depressive, and anxious symptoms at baseline and at six months following admission. Insight was measured with the Scale to assess Unawareness of Mental Disorder. FEP participants were categorized as a function of their medication adherence at six months into poor (n=16), partial (n=11) and full-adherence (n=61) groups. **Results:** No significant group differences in insight emerged at baseline. However, at six months, the poor-adherence group displayed worse insight relative to the partial-adherence group, while the full-adherence group displayed the best insight. At baseline, the partial-adherence group showed significantly higher positive symptoms relative to the other two groups. At month six, positive symptom severity was lowest in the full-adherence group, greatest in the poor-adherence group, with the partial-adherence group falling between the two. **Conclusions:** These results add to a growing literature showing a significant association between insight and medication adherence. Interestingly, insight improvement following the first six months of treatment was more strongly associated with medication adherence than baseline insight, suggesting a promising window of opportunity to enhance insight.

Key Words: Cognition, Insight, Psychosis, Schizophrenia, Treatment Adherence

Introduction

Medication adherence represents an essential component of sustained symptomatic remission and, ultimately, of a successful functional recovery in schizophrenia (1-3). Several factors have been shown to negatively affect medication adherence, including poor insight, psychopathology, substance use, treatment side effects (4-6), initial refusal and level of family support among others (7). In chronic schizophrenia, the association between insight and medication adherence in particular has been firmly established (6, 8, 9).

Some studies have investigated the relationship between insight and adherence to medication during the early stages of antipsychotic treatment in a first-episode psychosis (FEP). Mutsatsa et al. (10) found that lack of insight measured as soon as possible after admission to hospital was a significant predictor of poor adherence in 101 participants with a FEP. In a study by Kamali et al. (11), lack of insight at baseline was associated with nonadherence at six months in first-episode schizophrenia. Most recently, Perkins et al. (12) observed a trend for an association between poor insight at

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Clinical Implications

Our tripartite organization of adherence, which was similar to the approach developed by Hayward et al. (32) and applied in FEP by Coldham et al. (15), revealed a subgroup of patients with good medication adherence who displayed the best insight and fewest positive and negative symptoms after six months in a specialized care program. In comparison, FEP participants with partial adherence or poor adherence displayed significantly worse insight, and positive and negative symptoms after six months. Amador has suggested (33) that the period following the first episode of psychosis should be targeted as the most promising window of opportunity to enhance insight at a time when psychotic symptoms are possibly more amenable to cognitive behavioral therapeutic interventions (34, 35). In that sense, it is interesting to note that Lincoln and collaborators, as part of their exhaustive review on the long-term consequence of poor insight (8), have concluded that poor insight is associated with early-treatment adherence, yet its association with long-term adherence remains unclear. This is further supported by the observation that patients who reject the idea of medication at the time of the first assessment for entry to treatment are eleven times more likely to become nonadherent to medication six months later (7). Future studies may examine longitudinally levels of insight and medication adherence throughout the "critical period" following a first episode of psychosis.

baseline and nonadherence to medication over the following year in a large cohort (n=119) of people with first-episode schizophrenia spectrum disorders.

Two recent longitudinal studies have shown that insight improves during the first few months of treatment following admission to a specialized care program for a FEP (13, 14). The first study (13) observed significant improvement in insight three months post-baseline in a cohort of 180 people with a FEP. The second study, a longitudinal study of 181 FEP participants, examined level of insight at admission and after one, two, three, six, nine and twelve months of treatment (14). The authors observed that insight significantly improved very early on within the first two months of treatment. This early improvement in insight raises some questions about the association between insight level and medication adherence in FEP.

Two studies have examined change in insight over time and its association to medication adherence in FEP. First, in a cohort of 186 FEP patients, Coldham et al. (15) examined insight level at baseline and after one year using question G12 of the Positive and Negative Syndrome Scale (PANSS). After separating FEP participants into nonadherence, inadequate-adherence and good-adherence subgroups, the authors observed poor insight in nonadherent patients at both time points. Novak-Grubic and Tavcar (16) also examined insight level longitudinally and observed that level of insight at discharge from hospital, but not at intake, was a significant predictor of treatment nonadherence one year later. Although the results of these two longitudinal studies diverge, they nonetheless suggest that the strength of the association between insight and medication adherence may change over time.

The present study examined insight at baseline and after six months following admission to a specialized program for FEP. We administered a brief measure of insight consisting of the first three items from the Scale to assess Unawareness of Mental Disorder (SUMD) (17), which taps awareness of: 1) mental illness; 2) response to treatment; and, 3) need for treatment. A full clinical assessment, including the evaluation of medication adherence, was also performed at these two time points. In light of previous findings, we hypothesized that full medication adherence would be associated with better insight at baseline, but more strongly after six months of treatment.

Subjects and Methods

First-Episode Psychosis Participants

Eighty-eight FEP patients (56 males, 32 females) were recruited from the Douglas Institute's Prevention and Early Intervention for Psychoses Program (PEPP-Montreal) to participate in this study. The PEPP-Montreal is a specialized, early-intervention service with integrated clinical, research, and teaching modules. Briefly, the program involves a comprehensive approach with intensive medical and psychosocial management provided primarily through modified case management. Pharmacotherapy begins with a second-generation antipsychotic medication (olanzapine, risperidone, or quetiapine) within the recommended doses for a period of four to six weeks followed by an assessment of therapeutic response. In case therapeutic response is suboptimal, or side effects are noticed, an alternate second-generation antipsychotic medication is prescribed. In general, once the patient is in the PEPP program, the decisions regarding medication are made through a process of informing the patient and his/her family about the need for medication, and the choices available with their respective benefits and risks, and then, jointly, the decision is made. While specific treatment for psychosis begins with the initiation of antipsychotic medication, patients who initially refuse drug therapy are still provided with case management, support, and education along with their families. This

Table 1 **Sociodemographic Data of Poor-Adherence, Partial-Adherence, and Full-Adherence FEP Groups. (Number of participants included [n] for each variable where different from sample.)**

	Poor Adherence (n=16)	Partial Adherence (n=11)	Full Adherence (n=61)	Analysis		
				Statistic	df	p
Sociodemographic Variables						
Age (years)	22.4 (3.3)	22.3 (4.2)	22.6 (4.3)	F=.05	2, 85	0.95
Education	11.2 (2.1)	10.9 (2.5)	11.8 (2.2)	F=1.08	2, 85	0.35
Gender (M/F)	12/4	8/3	36/25	$\chi 2$=1.85	2	0.40
Patient SES†	3.9 (1.1)	3.4 (1.6)	3.4 (1.2) [59]	$\chi 2$=2.89	2	0.24
Parental SES†	3.3 (1.3) [15]	2.8 (1.2) [9]	2.8 (1.0) [52]	$\chi 2$=2.91	2	0.23
Diagnostic				$\chi 2$=6.03	4	.20
Schizo. spectrum	10	11	40			
Affective psychosis	5	0	15			
Psychosis NOS	1	0	6			
Symptoms						
SAPS Baseline	30.8 (12.4)	45.4 (19.5)	32.2 (14.0)	F=4.21	2, 85	0.02*
SAPS 6 months	16.3 (18.2)	13.3 (13.2)	5.8 (8.1)	F=6.65	2, 85	0.002*
SANS Baseline	28.8 (15.2)	34.9 (12.3)	27.0 (14.4)			
SANS 6 months	28.5 (18.1)	29.3 (12.7)	19.0 (13.8)			
CDS Total baseline	5.7 (6.1)	6.9 (4.1)	6.3 (6.1)			
CDS Total at 6 months	2.6 (4.6)	4.6 (4.3)	2.4 (3.7)			
HAS Total baseline	8.4 (8.7)	11.1 (6.5)	10.6 (7.8)			
HAS Total at 6 months	4.6 (6.5)	5.6 (3.9)	3.5 (3.9)			
Adherence to medication‡						
6 months	1.0 (1.0)	3.0 (0.0)	4.0 (0.0)	F=350.5	2, 85	<0.001
Medication Type of antipsychotic at 6 months (# cases)				$\chi 2$=9.82	14	0.78
Risperidone	4	2	15			
Olanzapine	6	4	26			
Quetiapine	3	1	4			
Haldol	0	1	1			
Risperidone Inj.	0	2	8			
Clozapine	0	0	1			
Paliperidone	0	0	1			
None	3	1	5			

M=male; F=female; SES=socioeconomic status; SAPS=Scale for the Assessment of Positive Symptoms; SANS=Scale for the Assessment of Negative Symptoms; CDS=Calgary Depression Scale; HAS=Hamilton Anxiety Scale. *Significant at $p<0.05$. †Hollingshead Parental Socio-Economic Status, in which 1=highest and 5=lowest. ‡Medication adherence average over six months: 0 (never adherent), 1 (very infrequently adherent), 2 (sometimes adherent), 3 (quite often adherent), 4 (always adherent). Post hoc analyses revealed all three groups differed from one another (all p's<0.001).

may extend for weeks and, occasionally, several months. In addition to pharmacotherapy, case managers provide individualized supportive psychotherapy and education to patients with one of the aims being an increase in awareness (i.e., insight) of the nature of their symptoms. Patients aged 14 to 30 years from the local catchment area, suffering from either affective or nonaffective psychosis, who had not taken antipsychotic medication for more than one month, were consecutively admitted to the program as either inpatients or outpatients. There is no competing service, and treatment is publicly funded.

Clinical and Demographic Data

All FEP participants underwent a comprehensive clinical evaluation that included the Scale for the Assessment of Positive Symptoms (SAPS) (18), the Scale for the Assessment of Negative Symptoms (SANS) (19), the Hamilton Anxiety Scale (anxiety) (20), and the Calgary Depression Scale (depression) (21). Total scores on these measures were used in all analyses. Clinical insight was measured using a brief version of the SUMD (22). For the purposes of this report, we limited our exploration of the SUMD to the first three items that were then combined into a single measure: Q1—awareness of a mental illness; Q2a—awareness of response to medication; and, Q2b—belief that the patient needs medication or would benefit from it. Insight was defined as the global (summed) score of the three items. Clinical and insight measures were taken at baseline, month 1, month 2, month 3 and month 6, but for the present report, we limited our analyses to the baseline and month 6 data. Symptom and insight ratings were performed by research assistants and graduate students (intra-class correlation coefficient [ICC]=0.75), who received extensive training and supervision, with reliability measured at least once a year. Symptom raters were not involved with the treatment of the patient.

Treatment-Adherence Measure

Medication adherence was measured at six months following admission using a 5-point scale (0=never adherent, 1=very infrequently adherent, 2=sometimes adherent, 3=quite often adherent, 4=always adherent) based on composite information obtained from patients and case managers (2). Patients were asked how often they missed a dose over the past month and adherence was calculated as a percent of prescribed doses taken. Similar methodology (i.e., asking patients how often they missed a dose over the past month) was employed by clinical staff and adherence recorded as a percentage in clinical notes. Correlational analyses among scores based on information obtained from patients and clinical notes, and a more objective measure of pill counting, were available for a subset of the sample (n=50) (23). A pill count entailed counting the number of pills left in the bottle and subtracting these from the number given when the prescription was filled, yielding the number of doses taken since the patient started taking the prescription (usually determined as the time when the previous prescription was set to run out). Pill count correlated highly to patient ($r=.91$, $p<.001$), family ($r=.69$, $p<.001$) and case manager ($r=.87$, $p<.001$) reports of adherence. We defined full adherence as a rating of 4 (76%–100%), partial adherence as a rating of 3 (51%–75%), and poor adherence as a rating of 2 or less (≤50%). Medication adherence was recorded by the same raters who performed the insight and symptom ratings; however, given that adherence ratings reflect a composite of both subjective (patients, case managers, clinical notes) and objective sources (pill counting in some cases) we consider this of minimal significance.

Results

Demographical and Clinical Data

Applying the group definition of adherence to our sample of 88 FEP participants, we identified a group of 61 patients with full adherence, a group of 11 patients with partial adherence, and a group of 16 patients with poor adherence, at 6 months following admission into the program. Table 1 presents the sociodemographical variables for the three adherence FEP groups. The three medication-adherence groups did not differ significantly with respect to age, gender, education, and patient or parental socioeconomic status (SES). There were no significant between-group differences in the type of diagnosis (schizophrenia spectrum vs. affective psychosis) or the type of antipsychotic medication taken at the time of this study.

Insight Data

The brief global measure of insight was examined using a repeated measures ANOVA with time as the within-group variable and group association as the between-group variable. This analysis revealed a significant Time X Group interaction ($F[2, 85]=3.92$, $p=.02$). Simple effects determined that there were no significant group differences at baseline, but that all groups significantly differed from one another at six months (all p values <0.01). Within-group differences revealed only the full-adherent group improved in insight ($p<0.001$), while the partial-adherent group ($p=0.14$) and poor-adherent group ($p=0.27$) did not improve significantly in insight over the six months (see Table 2 and Figure 1). To examine what item(s) was driving the overall effect, the individual items from SUMD (Q1, Q2a, and Q2b) were analyzed using univariate one-way ANOVAs. The results complemented the results from the global measure. Specifically, scores on the three items did not differ among the three

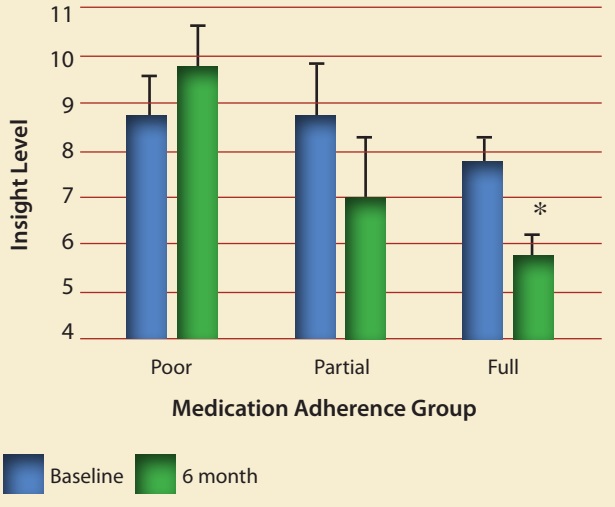
Table 2 Summed Score on the Three General Questions of the Scale for the Unawareness of Mental Disorder (SUMD) at Baseline and Six Months in the Three FEP Adherence Groups

	Poor Adherence	Partial Adherence	Full Adherence	ANOVA		
				F	df†	p
SUMD index baseline	8.8 (3.3)	8.7 (3.8)	7.8 (3.9)	0.63	2, 146	0.53
SUMD index month 6	9.8 (3.4)	7.0 (4.2)	5.8 (3.0)	7.10	2, 146	0.001*
Q1 baseline	3.3 (1.2)	3.0 (1.2)	2.9 (1.4)	0.39	2, 85	0.68
Q1 month 6	3.1 (1.3)	2.4 (1.5)	2.2 (1.2)	3.20	2, 85	0.05*
Q2a baseline	2.9 (1.6)	3.0 (1.5)	2.4 (1.4)	1.08	2, 85	0.35
Q2a month 6	3.5 (1.4)	2.1 (1.7)	1.6 (1.0)	16.52	2, 85	<0.001*
Q2b baseline	2.6 (1.3)	2.7 (1.4)	2.4 (1.4)	0.40	2, 85	0.67
Q2b month 6	3.3 (1.4)	2.6 (1.6)	2.0 (1.3)	5.43	2, 85	0.006*

*Significant at p<0.05; †df for the global scores was a pooled value calculated during the simple effects analysis.

groups at baseline, but by six months, significant group differences emerged (see Table 2). Items Q2a and Q2b, more than Q1, appeared to be driving the group differences observed with the global insight measure based on the level of significance attained. Post hoc analyses for Q1 revealed a significant difference between the full-adherent group and poor-adherent group (p=0.04); the other two comparisons were not significantly different (p=0.35 for partial-adherent vs. poor-adherent and p=0.87 for partial-adherent vs. full-adherent). For Q2a, the full-adherent group significantly differed from both the partial-adherent group (p=0.007) and poor-adherent group (p<0.001); the partial-adherent and full-adherent groups did not significantly differ (p=0.46). Finally, for Q2b, there was a significant difference between the full-adherent group and poor-adherent group (p=0.005); the other two comparisons were not significantly different (p=0.39 for partial-adherent vs. poor-adherent and p=0.46 for partial-adherent vs. full-adherent).

Figure 1 Mean Ratings for Insight Levels (Summed Score of Items 1, 2a and 2b from the SUMD) at Baseline and after Six Months as a Function of Medication-Adherence Group (Poor, Partial, Full)



*p<.05, full-adherent less than partial-adherent and poor-adherent. Higher scores indicate poorer insight.

Symptom Data

Positive and negative symptoms, anxiety and depression were examined using a repeated measures ANOVA with time as the within-group variable and group association as the between-group variable. The examination of positive symptoms revealed a significant interaction (F[2, 85]=4.80, p=0.01). Within-group analyses revealed all three groups significantly improved over time (all p values <0.001). Simple effects revealed that, at baseline, the full-adherence and poor-adherence groups did not differ (p>0.05), while both groups were significantly less symptomatic than the partial-adherence group (both p values <0.01). At six months, the full-adherence group was significantly less symptomatic than the other two groups (both p values <0.01); moreover, the partial-adherence group was significantly less symptomatic than the poor-adherence group (p<0.05). There were no significant interactions for negative symptoms (F[2, 8]=1.48, p=0.23), anxiety (F[2, 85]=1.06, p=0.35), or depression (F[2,

85]=0.36, p=0.70). Interestingly, an exploratory analysis of the negative symptoms revealed only the full-adherence group significantly improved over time (p<0.001). Furthermore, at six months, negative symptom severity of the full-adherence group was significantly less than that of the partial-adherence and poor-adherence groups (both p values <0.01), while the latter two groups did not differ from each other (p>0.05).

Discussion

This study examined the impact of early changes in insight following admission to a specialized program for a first-episode psychosis (FEP) on medication adherence six months later. In our FEP cohort, we identified 16 (18%) poor-adherence, 11 (13%) partial-adherence and 60 (69%) good-adherence participants. Exploration of insight level at baseline based on the first three items of the SUMD revealed poor insight across all medication adherence groups. The same assessment of insight six months later revealed significant differences across the three groups, with the full-adherence group displaying the best insight, followed by the partial-adherence group, with the lowest insight in the poor-adherence group. Moreover, insight improved from baseline to six months in the good-adherence group only. The FEP participants with good medication adherence and good insight showed significant reductions in positive and negative symptomatology.

Rate of adherence to treatment in the present study is somewhat different from what has been reported in other studies. For instance, Coldham and colleagues (15) reported rates of nonadherence at 39%, inadequate adherence at 20% and good adherence at 41% after one year of treatment. Another study (11) reported that one-third of patients with a first episode of schizophrenia were nonadherent six months after admission. In this study, nonadherence was defined as taking medication less than 75% of the time. As such, this definition encompasses both the poor- and partial-adherence subgroups from the present study, which also amount to approximately one-third of our total FEP sample. The discrepancy in number of good-adherence patients reported at six months (about one-third of patients) and after one year (41% in Kamali et al. [11]) may suggest that, in some people with a FEP, medication adherence may diminish during months six to twelve.

Insight and Short-Term Adherence to Treatment

Adherence to treatment following a first episode of psychosis is an important factor for achieving symptomatic remission (2), as well as a positive functional outcome (1, 3). Adherence to treatment, however, is a complex construct that is likely multidetermined by environmental, medication-related and patient-related factors (4). With respect to the latter, several dimensions of cognition seem to impact on adherence to antipsychotic treatment. At the metacognitive level, awareness of one's illness (24, 25), beliefs about the need for treatment and benefits of antipsychotic medication have a direct influence on drug attitudes (26) and, ultimately, on medication adherence (27). The present data support this notion and further indicate that even partial nonadherence to treatment interacts with insight over the first six months of a FEP. The finding that insight at baseline did not associate to adherence suggests that it is not a useful indicator of adherence at the six-month follow-up. This may suggest that: 1) in some patients, insight is a malleable construct amenable to improvement through sustained antipsychotic use; 2) treatment compliance may promote the maintenance of good insight in patients who show good insight at the initial assessment; and, 3) continuous (six month) treatment noncompliance may be a risk factor for poor insight, rather than poor insight predicting nonadherence to treatment. The ability to recognize symptoms as abnormal and attributable to a mental disorder may be important for patients' core beliefs about medication benefits and their willingness to adhere to treatment. Improving patients' ability to recognize the importance of treatment on the progression of their illness early on (within the first six months) may have a positive influence on future adherence in FEP.

Insight and Symptomatic Response to Treatment

It has been suggested that level of insight could partly reflect the degree of response to treatment (10). In the current work, FEP participants with good adherence to treatment displayed the best insight and fewest positive and negative symptoms at six months, which supports this notion. The positive symptom result is in line with several studies reporting poorer insight with greater positive symptoms in the early stages of a FEP (11, 14, 15). A body of literature looking more closely at specific positive symptoms, most often delusions, in tandem with insight has argued that poor insight may represent a particular type of delusion, a "delusion of health," characterized by the fixed, false and impermeable belief that they are not ill. Our data support the idea that positive symptoms are an integral part of insight, adding to meta-analytic evidence for a modest, yet consistent, coupling between these constructs in schizophrenia (28), and to observations that this relation is pronounced in acute samples.

Our FEP participants with good medication adherence and the best insight also showed the fewest negative symptoms, supporting previous results in FEP (10). A modest relationship between negative symptoms and insight in

schizophrenia has been established in the literature (28). The clinical presentation of negative symptoms, including apathy, difficulty in experiencing pleasure, avolition and social withdrawal, may lead to impairments in insight by reducing patients' ability to understand the need for treatment and/or their motivation to take it (29). Taken together, both poor insight and severe psychopathology appear to be early indicators of nonadherence to medication in FEP.

Limitations and Future Studies

Our longitudinal study design captured insight and medication adherence in patients with a first-episode psychosis at admission to hospital and after six months of treatment. Changes in insight, symptoms and adherence (if any) within these six months might have been illuminated using shorter time periods (e.g., including the one-month, two-month and three-month assessments). Future works may consider the short-term progression and interaction of these variables. It has been suggested that measurement of patients' awareness of the need for treatment and subsequent adherence to medication may be tautological. Although a link between the two has been borne out in the literature, one's realization of the benefits of medication does not directly correspond to adherence to treatment. In fact, adherence is likely multidetermined (10, 30). Our data indicate that treatment discontinuation is related to several dimensions of insight, as well as the severity of positive and negative symptoms.

One important consideration relates to changes in insight and medication adherence from early to more chronic phases of the disorder. There is a growing recognition of the role of poor insight in the reemergence of symptoms and as a trigger for relapse. Cognitive behavioral interventions that target core belief systems may also help to improve patients' beliefs about their condition and the need for treatment, and promote a positive symptomatic outcome. It should be noted that other factors may contribute to medication infidelity, including suboptimal treatment response (27), negative attitudes toward medication (10), alcohol and drug misuse (11), and internal premorbid characteristics and developmental achievements (31). Finally, in some patients continuous antipsychotic treatment may not be necessary to achieve a favorable outcome. For example, a recent twenty-six year follow-up study demonstrated that some patients with psychosis who discontinued antipsychotic treatment for extended periods also experienced periods of recovery (31).

Conclusions

In summary, our tripartite organization of adherence, which was similar to the approach developed by Hayward et al. (32) and applied in FEP by Coldham et al. (15), revealed a subgroup of patients with good medication adherence who displayed the best insight and fewest positive and negative symptoms after six months in a specialized care program. In comparison, FEP participants with partial adherence or poor adherence displayed significantly worse insight, and positive and negative symptoms after six months. Amador has suggested (33) that the period following the first episode of psychosis should be targeted as the most promising window of opportunity to enhance insight at a time when psychotic symptoms are possibly more amenable to cognitive behavioral therapeutic interventions (34, 35). In that sense, it is interesting to note that Lincoln and collaborators, as part of their exhaustive review on the long-term consequence of poor insight (8), have concluded that poor insight is associated with early-treatment adherence, yet its association with long-term adherence remains unclear. This is further supported by the observation that patients who reject the idea of medication at the time of the first assessment for entry to treatment are eleven times more likely to become nonadherent to medication six months later (7). Future studies may examine longitudinally levels of insight and medication adherence throughout the "critical period" following a first episode of psychosis.

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References

1. Malla AK, Norman RM, Manchanda R, Townsend L. Symptoms, cognition, treatment adherence and functional outcome in first-episode psychosis. Psychol Med 2002;32(6):1109-1119.
2. Malla A, Norman R, Schmitz N, Manchanda R, Bechard-Evans L, Takhar J, et al. Predictors of rate and time to remission in first-episode psychosis: a two-year outcome study. Psychol Med 2006;36(5):649-658.
3. Ascher-Svanum H, Faries DE, Zhu B, Ernst FR, Swartz MS, Swanson JW. Medication adherence and long-term functional outcomes in the treatment of schizophrenia in usual care. J Clin Psychiatry 2006;67(3):453-460.
4. Fenton WS, Blyler CR, Heinssen RK. Determinants of medication compliance in schizophrenia: empirical and clinical findings. Schizophr Bull 1997;23(4):637-651.
5. Young JL, Spitz RT, Hillbrand M, Daneri G. Medication adherence failure in schizophrenia: a forensic review of rates, reasons, treatments, and prospects. J Am Acad Psychiatry Law 1999;27(3):426-444.
6. Lacro JP, Dunn LB, Dolder CR, Leckband SG, Jeste DV. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. J Clin Psychiatry 2002;63(10):892-909.
7. Rabinovitch M, Bechard-Evans L, Schmitz N, Joober R, Mall A. Early predictors of nonadherence to antipsychotic therapy in first-episode psychosis. Can J Psychiatry 2009;54(1):28-35.

8. Lincoln TM, Lullmann E, Rief W. Correlates and long-term consequences of poor insight in patients with schizophrenia. A systematic review. Schizophr Bull 2007;33(6):1324-1342.
9. Lin IF, Spiga R, Fortsch W. Insight and adherence to medication in chronic schizophrenics. J Clin Psychiatry 1979;40(10):430-432.
10. Mutsatsa SH, Joyce EM, Hutton SB, Webb E, Gibbins H, Paul S, et al. Clinical correlates of early medication adherence: West London first episode schizophrenia study. Acta Psychiatr Scand 2003;108(6):439-446.
11. Kamali M, Kelly BD, Clarke M, Brownde S, Gervin M, Kinsella A, et al. A prospective evaluation of adherence to medication in first episode schizophrenia. Eur Psychiatry 2006;21(1):29-33.
12. Perkins DO, Gu H, Weiden PJ, McEvoy JP, Hamer RM, Lieberman JA; Comparison of Atypicals in First Episode study group. Predictors of treatment discontinuation and medication nonadherence in patients recovering from a first episode of schizophrenia, schizophreniform disorder, or schizoaffective disorder: a randomized, double-blind, flexible-dose, multicenter study. J Clin Psychiatry 2008;69(1):106-113.
13. Mintz AR, Addington J, Addington D. Insight in early psychosis: a 1-year follow-up. Schizophr Res 2004;67(2-3):213-217.
14. Buchy L, et al. A 12-month outcome study of insight and symptom change in first-episode psychosis. Early Interv Psychiatry. In press 2009.
15. Coldham EL, Addington J, Addington D. Medication adherence of individuals with a first episode of psychosis. Acta Psychiatr Scand 2002;106(4):286-290.
16. Novak-Grubic V, Tavcar R. Predictors of noncompliance in males with first-episode schizophrenia, schizophreniform and schizoaffective disorder. Eur Psychiatry 2002;17(3):148-154.
17. Amador XF, Strauss DH, Yale SA, Flaum MM, Endicott J, Gorman JM. Assessment of insight in psychosis. Am J Psychiatry 1993;150(6):873-879.
18. Andreasen NC. Scale for the assessment of positive symptoms (SAPS). Iowa City (IA): The University of Iowa; 1984.
19. Andreasen NC. Modified scale for the assessment of negative symptoms (SANS). Iowa City (IA): The University of Iowa; 1984.
20. Riskind JH, Beck AT, Brown G, Steer RA. Taking the measure of anxiety and depression: validity of the reconstructed Hamilton scales. J Nerv Med Dis 1987;175(8):474-479.
21. Addington D, Addington J, Schissel B. A depression rating scale for schizophrenics. Schizophr Res 1990;3(4):247-251.
22. Amador XF, Flaum M, Andreasen NC, Strauss DH, Yale SA, Clark SC, et al. Awareness of illness in schizophrenia and schizoaffective and mood disorders. Arch Gen Psychiatry 1994;51(10):826-836.
23. Cassidy CM, Rabinovitch M, Joober R, Malla A. Is any one method of measuring medication adherence in first-episode psychosis better than others? Schizophr Res 2008;98(Suppl 1):81.
24. Cuffel BJ, Alford J, Fischer EP, Owen RR. Awareness of illness in schizophrenia and outpatient treatment adherence. J Nerv Ment Dis 1996;184(11):653-659.
25. Kemp R, David A. Psychological predictors of insight and compliance in psychotic patients. Br J Psychiatry 1996;169(4):444-450.
26. Rocca P, Crivelli B, Marino F, Mongini T, Portaleone F, Bogetto F. Correlations of attitudes toward antipsychotic drugs with insight and objective psychopathology in schizophrenia. Compr Psychiatry 2008;49(2):170-176.
27. Perkins DO, Johnson JL, Hamer RM, Zipursky RB, Keefe RS, Centorrhino F, et al.; HGDH Research Group. Predictors of antipsychotic medication adherence in patients recovering from a first psychotic episode. Schizophr Res 2006;83(1):53-63.
28. Mintz AR, Dobson KS, Romney DM. Insight in schizophrenia: a meta-analysis. Schizophr Res 2003;61(1):75-88.
29. Nakano H, Terao T, Iwata N, Hasako R, Nakamura J. Symptomatological and cognitive predictors of insight in chronic schizophrenia. Psychiatry Res 2004;127(1-2):65-72.
30. David AS. Commentary on: "Is insight into psychosis meaningful?" Journal of Mental Health 1997;7:579-583.
31. Harrow M, et al. Do all schizophrenia patients need to use antipsychotic medications throughout their lifetimes: a 26-year multi-followup. Schizophr Bull 2009;35(Suppl 1):344.
32. Hayward P, et al. Medication self-management: a preliminary report on an intervention to improve medication compliance. J Ment Health 1995;4:511-517.
33. Amador X. I am not sick I don't need help! 2nd edition. Peconic (NY): Vida Press; 2007.
34. Beck AT, Rector NA, Stolar NM, Grant PM. Schizophrenia: cognitive theory, research, and therapy. New York: Guilford Press; 2009.
35. Rathod S, Kingdon D, Smith P, Turkington D. Insight into schizophrenia: the effects of cognitive behavioural therapy on the components of insight and association with sociodemographics--data on a previously published randomised controlled trial. Schizophr Res 2005;74(2-3):211-219.