Clinical correlates of early medication adherence: West London first episode schizophrenia study


Objective: Little is known about factors that mediate adherence with medication during the early stages of antipsychotic treatment in schizophrenia. This study sought to identify factors that may be associated with medication adherence in first-episode schizophrenia.

Method: In 101 patients, adherence was assessed along with potentially relevant variables, including attitudes toward medication, insight, substance misuse, side effects and psychopathology.

Results: In a linear regression analysis, negative attitudes toward medication and a relative lack of insight contributed significantly towards poor adherence. Although poorly adherent patients had significantly higher scores on negative and disorganization syndromes, these did not contribute significantly towards adherence. Adverse medication side effects, subjective well-being and substance misuse showed no significant association with adherence.

Conclusion: At the initiation of drug treatment, attitudes toward medication and insight appear more relevant to medication adherence than side effects. Adherence appears to reflect a complex interaction of influences, which may change over time.

Introduction

Adherence to medication plays a key role in determining the degree of response to antipsychotic medication during different phases of schizophrenia (1). In people with chronic schizophrenia, estimated relapse rates because of non-adherence with medication are as high as 50% for patients during the year following discharge (2). In the early stages of the illness, patients seem to be more responsive to treatment irrespective of the antipsychotic drug used (3), but defaulting on medication is a common problem. In this population, the discontinuation of antipsychotic medication may have adverse implications for the subsequent course of the illness, particularly a greater likelihood of readmission to hospital (4, 5). Therefore, identification of the factors relevant to adherence during the initial period of care may be particularly critical.

Previous studies have identified a range of factors contributing to poor adherence with antipsychotic medication, such as adverse side effects, more severe illness and substance misuse (2, 6, 7). The majority of these studies have been carried out on samples of chronic patients, but several have prospectively examined samples of patients following a first episode of psychosis (5, 8–12). Factors such as poor insight and negative attitudes toward medication have also been implicated, and these factors have been reported in one first episode study (11). In a sample of 59 first episode psychotic patients, Kampman and colleagues (11) reported that both insight and attitudes towards medication were the sole determinants of medication adherence during the early psychotic stage of the illness. Both insight and attitudes toward medication are potentially amenable to change (13) and the examination of their impact on adherence during the early stages of...
medication taking is important as it has the potential to inform the shaping of specific psychological interventions to enhance medication adherence.

Aims of study
This study sought to examine systematically possible associations between early medication adherence in first episode schizophrenia and a range of illness, treatment and personal variables such as insight, psychopathology, substance misuse, side effects, and attitudes. Additionally, this study examined the potential association between patients’ subjective well being and adherence with antipsychotic treatment, a domain that has not been studied previously in first episode schizophrenia.

Material and methods
Patients were recruited as part of an on-going prospective study of first episode schizophrenia in West London (14, 15). The patients eligible for the study were aged between 16 and 55 years, were presenting to mental health services with schizophrenia or a schizophreniform psychosis for the first time and had received no more than 12 weeks of antipsychotic medication. Patients who had a primary diagnosis of organic brain syndrome, learning disability, or substance misuse were excluded from the study. Data on treatment adherence were obtained from 101 patients. Each of these fulfilled Diagnostic Statistical Manual IV (DSM IV) diagnostic criteria for a diagnosis of schizophrenia or schizophreniform disorder which was subsequently confirmed at a diagnostic review by two senior clinicians (EMJ, TREB). All but twelve patients were in-patients at the time of assessment. The catchment area for the study comprised inner London areas and a more suburban, outer London area. Approval to conduct the study was obtained from Riverside, Merton, Sutton and Wandsworth, Kingston and Richmond, Ealing, Hammersmith and Fulham Research Ethics Committees.

Assessments
Assessments were performed as soon as possible during admission to hospital at a time when they were able to give informed consent and complete the rating scales. The range and severity of psychopathology were assessed using the Scale for the Assessment of Positive Symptoms (SAPS) (16) and the Scale for the Assessment of Negative Symptoms (SANS) (17).

Adherence with medication was assessed using the seven point Compliance Rating Scale (CRS) (18) as follows: 1, complete refusal; 2, partial refusal (e.g. refused depot) or only accepts minimum doses; 3, accepts only because compulsory or very reluctant requires persuasion or question need often; 4, occasional reluctance (e.g. question need once a week); 5, passive acceptance; 6, moderate participation, some knowledge and interest in medication and no prompting required; 7, active participation readily accepts, and shows some responsibility for regimen. In all instances, this global measure of adherence was based on reports from those people most closely involved with the patients’ care at the time. These included the primary nurse, doctors, relatives and carers. Any relevant information in the patients’ case-notes and prescription cards was also taken into consideration.

The rating of medication influences (ROMI) (19) was used to assess attitudes toward medication. This scale is in two parts. The first assesses positive attitudes, and comprises seven explanations of good compliance: perceived benefit, positive relationship with clinician, positive relationship with therapist, positive family belief in medication, relapse prevention, pressure to take medication and fear of hospitalization. The second part assesses negative attitudes toward medication and comprises 12 items: perceived lack of benefit, negative relationship with clinician, negative relationship with therapist, practitioner opposed to medication, family/friends opposed to medication, problems with access to treatment, stigma related to medication, financial obstacles, substance abuse, denial of illness, belief that medication is unnecessary, distressed by side effects, and desires hospitalization.

The schedule for the assessment of insight (SAI) (20) was used to assess three components of insight: awareness of illness; the capacity to re-label psychotic experiences; and the need for treatment adherence.

Subjective antipsychotic side effects were assessed using the Liverpool University Side Effects Rating Scale (LUNSERS) (21) which is based on the UKU side effects rating scale (22) and incorporates psychological, neurological, autonomic, hormonal and miscellaneous side effects. The subjective experience of antipsychotic drug treatment was assessed using the Subjective Well-being under Neuroleptics Scale (SWN) (23) which incorporates: emotional regulation; self control; mental functioning; social integration; and physical functioning. Movement disorders were assessed using the Abnormal Involuntary Movements Scale.
(AIMS) (24), the Extrapyramidal Side Effects Rating Scale (EPSE) (25) and the Barnes Akathisia Rating Scale (BARS) (26). The presence of akathisia was defined as a score of 2 or more on the global item of the BARS scale, and the presence of parkinsonism was defined as a score of 3 or more on the EPSE scale. Dyskinesia was determined as present at two levels of severity, as follows: (1) Mild dyskinesia, which was defined as the presence of a rating of ‘mild’ on any AIMS body site item. (2) Fulfilling RDC severity criteria for tardive dyskinesia (27), with the presence of at least a ‘moderate’ rating in one or more body areas, or ‘mild’ movements in two or more body areas.

Lifetime reports of alcohol and non-alcohol substance use were recorded using the Substance Use Rating Scale, patient version: SURSp (28).

Duration of untreated psychosis, which in this study was defined as the time between the onset of psychosis and treatment initiation, was estimated by gathering information from the patients and their case notes as well as interviews with relatives or carers (7).

Statistical analysis

The Statistical Package for Social Science (SPSS), version 10 was used. Group difference was analyzed with independent *t*-tests with degrees of freedom adjusted according to Levene’s test for equality of variance and correlations were determined using Pearson’s product moment *r*. Explanatory variables for compliance with antipsychotic medication were determined using multiple linear regression techniques.

Results

For the majority of in-patients (85%) in the sample, the research assessments were completed within 3 weeks of admission to hospital. A median split based on the CRS scores generated a ‘good adherence’ subgroup scoring 5 (passive acceptance) or more, and a ‘poor adherence’ subgroup scoring of 4 (occasional reluctance or questions need) or less. The demographic details and the clinical characteristics of these subgroups are shown in Table 1. There were no significant differences with respect to age, gender and the proportion of patients receiving atypical antipsychotic drugs.

Adherence with medication and severity of illness

Scores for positive, disorganization and negative syndromes of schizophrenia (29) were calculated for each patient by summing up the SAPS and SANS global subscales score pertaining to each factor (30). Comparisons of the two adherence groups on these syndrome scores revealed a significant difference between the two groups. The poor adherence group showed significantly higher mean scores on the negative and disorganization syndromes than the good adherence group (see Table 2).

Attitudes and adherence

On the ROMI negative attitudes subscale, the poor adherence group had a significantly higher mean score (see Table 2) than the good

<table>
<thead>
<tr>
<th>Variable</th>
<th>Good adherence</th>
<th>Poor adherence</th>
<th><em>t</em>/*χ² [df]</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>n</em></td>
<td>57</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Age in years: mean (SD)</td>
<td>25.23 (6.32)</td>
<td>27.77 (8.06)</td>
<td>0.08 [99], <em>P</em> = 0.30</td>
</tr>
<tr>
<td>Gender: <em>n</em> (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>47 (82.45)</td>
<td>32 (72.72)</td>
<td>1.38 [1], <em>P</em> = 0.24</td>
</tr>
<tr>
<td>Female</td>
<td>10 (17.54)</td>
<td>12 (27.27)</td>
<td></td>
</tr>
<tr>
<td>Prescribed antipsychotic medication: <em>n</em> (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional antipsychotic</td>
<td>26 (45.61)</td>
<td>18 (40.90)</td>
<td></td>
</tr>
<tr>
<td>Atypical antipsychotic</td>
<td>31 (54.38)</td>
<td>26 (59.09)</td>
<td>0.22 [1], <em>P</em> = 0.63</td>
</tr>
<tr>
<td>Side effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LUNSERS: mean total score (SD)</td>
<td>39.76 (20.54)</td>
<td>40.22 (25.29)</td>
<td>0.09 [82], <em>P</em> = 0.93</td>
</tr>
<tr>
<td>Presence of movement disorders: <em>n</em> (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>17 (28.8)</td>
<td>6 (13.63)</td>
<td>2.85 [1], <em>P</em> = 0.14</td>
</tr>
<tr>
<td>Akathisia</td>
<td>20 (35.08)</td>
<td>8 (18.18)</td>
<td>3.06 [1], <em>P</em> = 0.08</td>
</tr>
<tr>
<td>Dyskinesia: mild movements</td>
<td>13 (22.80)</td>
<td>6 (13.63)</td>
<td>1.13 [1], <em>P</em> = 0.28</td>
</tr>
<tr>
<td>Dyskinesia: RDC severity criteria</td>
<td>6 (10.52)</td>
<td>5 (11.36)</td>
<td>0.04 [1], <em>P</em> = 0.8</td>
</tr>
<tr>
<td>Lifetime alcohol misuse: <em>n</em> (%)</td>
<td>12 (21.05)</td>
<td>5 (11.36)</td>
<td>4.00 [2], <em>P</em> = 0.13</td>
</tr>
<tr>
<td>Lifetime non-alcohol misuse: <em>n</em> (%)</td>
<td>32 (56.14)</td>
<td>31 (70.45)</td>
<td>1.08 [1], <em>P</em> = 0.30</td>
</tr>
<tr>
<td>Duration of untreated psychosis: Mean log (10) weeks (SD)</td>
<td>1.51 (0.62)</td>
<td>1.35 (0.58)</td>
<td>1.22 [84], <em>P</em> = 0.22</td>
</tr>
</tbody>
</table>
adherence group, indicating that the poor adherence group expressed more negative attitudes towards medication. On the ROMI positive attitude subscale, the poor adherence group had a lower mean score than the good adherence group but this difference was not statistically significant (see Table 2).

Adherence and insight

On the SAI and its subscales, the good adherence group had significantly higher mean scores than the poor adherence group suggesting that the poor adherence group had significantly poorer insight (see Table 2).

Adherence and antipsychotic side effects

In the total sample, the proportions of patients with akathisia and parkinsonism were 27.7 and 22.8%, respectively. Mild dyskinesia was present in 18.8%, and the RDC severity criteria for tardive dyskinesia were fulfilled in 10.9% of the total sample. There were no significant differences between the good and poor adherence subgroups in the prevalence of akathisia, parkinsonism or non-neurological side effects (see Table 1). There were no significant differences between the groups on the measures of subjective well being (see Table 2).

Adherence and substance misuse

There were no significant differences between the two adherence groups in the proportion of patients reporting lifetime alcohol or non-alcohol substance misuse (see Table 1).

Linear regression analysis

Initially, a correlational analysis was carried out to examine associations of variables with adherence to medication. Negative attitudes toward medication correlated significantly with adherence ($r = 0.28, P < 0.01$). Total insight and its three domains significantly correlated with adherence to medication (total insight: $r = 0.55, P < 0.01$; awareness of illness: $r = 0.31, P < 0.01$; correct attribution of illness: $r = 0.31, P < 0.01$; need for treatment: $r = 0.82, P < 0.01$) In addition there was a trend level significant correlation between adherence and negative syndrome scores ($r = 0.19, P = 0.06$) and extrapyramidal side effects ($r = 0.17, P = 0.09$). No other significant relationship between adherence and the remaining variables was observed. To determine which of the significant variables predicted adherence with antipsychotic medication, a stepwise linear regression analysis was performed. Using adherence score as the dependent variable, the following independent variables scores were entered: total insight, ROMI negative attitudes toward medication, extrapyramidal side effects and negative syndrome. Only insight and negative attitudes toward medication contributed significantly towards adherence with antipsychotic medication. Together, these variables explained 27% of the variance in adherence (adjusted $R^2 = 0.271, F = 13.83, P < 0.001$).

Discussion

Adherence and attitudes towards treatment

The findings in this sample suggest that attitudes towards treatment are a major influence on...
Medication adherence in schizophrenia

Medication adherence in the early stages of antipsychotic drug treatment for first episode schizophrenia. Similar findings have been reported in samples of patients with chronic schizophrenia (13, 31–35) and recently in first episode psychosis (11). The ROMI scale, which was used to assess attitudes in this study, is based on the Health Belief Model (HBM) (36). The HBM posits that four main beliefs contribute to the likelihood of an individual adhering to prescribed medication. These belief factors are first, the perceived benefit of adhering to medication, secondly, the perceived barriers to adherence, thirdly, the perceived susceptibility to illness, and lastly, the perceived severity of outcome. Thus, if a patient perceives that the benefit of taking medication exceeds that of the cost, then the person is likely to adhere to treatment and vice versa. Some authors have argued that the HBM model may be more explanatory of adherence behaviour in schizophrenia than the concept of insight (37, 38).

Adherence and insight

In this study, the results of the regression showed that poor insight explained a significant proportion of non-adherence behaviour. This finding is in accord with earlier studies (31, 32, 35, 39–41) and the more recent study (11). Nevertheless, interpretation of these findings should take account of two points. First, the level of insight might partly reflect the degree of response to antipsychotic medication, albeit over the relatively brief period involved. In other words, a relatively limited clinical response and, therefore, poorer insight might be expected in those patients who have been less adherent with medication.

Secondly, there has been criticism of insight specifically in relation to its investigation as a factor contributing to adherence behaviour. If the perceived need for treatment is one of the components of insight, then examining the impact of such a component on adherence may be seen as tautological (38, 42). However, the relationship between acceptance of the need for treatment and adherence with medication may not be as circular as it first appears. David (43) has argued that stated intent (acceptance of the need for treatment) and actual adherence behaviour is not necessarily the same thing. Thus, a patient who reports good intentions about taking medication may not actually take it for a variety of other reasons.

Accepting the HBM as a valid explanatory model for adherence behaviour, it is possible to integrate the influence of insight. Poor insight could affect adherence behaviour by increasing the threshold for perceived threat, awareness of susceptibility to illness and appreciation of the benefits of treatment. Thus, a person who does not acknowledge the presence of psychotic symptoms or incorrectly attributes their symptoms may be less likely to seek medical help or adhere to medication.

Psychopathology and adherence

In this study, those patients who adhere poorly with medication showed a greater severity of disorganization and negative symptoms. This finding has been reported in several studies of chronic schizophrenia (20, 44, 45). It is plausible that those patients showing conceptual disorganization and more negative symptoms may show diminished levels of appreciation for the need for treatment and are less motivated to take medication.

Side effects and adherence

Our cross-sectional data do not allow us to unravel whether the emergence of side effects may have influenced subsequent medication adherence, or whether the presence of side effects is simply a reflection of good adherence. Nevertheless, the finding that the severity of side effects does not differ significantly between good and poor adherence groups suggests that they are not useful indicators of adherence during the early stages of antipsychotic treatment. Other investigators have reported similar findings (45, 46); although some studies in this area have found an association between these variables (11, 31, 47–49). Nevertheless, Sellwood and Tarrier (50) reviewed the evidence for a relationship between adherence and adverse side effects; they lamented the paucity of literature on the subject, and concluded that there were insufficient data to convincingly support such an association.

A possible explanation for the lack of predictive power of antipsychotic drug side effects for adherence behaviour in this study may relate to the reliability and validity of patients’ reports. First episode schizophrenic patients have experienced only a relatively short period of drug treatment and therefore may not readily distinguish medication side effects from symptoms of the illness. Following discharge and maintenance treatment in the community, patients may become more aware of, and less tolerant of, side effects, particularly if they interfere with their social and occupational functioning.

Alternatively, it may be pertinent that the majority of the sample (57%) was receiving newer, atypical antipsychotics, with slightly more
patients in the good adherence group (32% of the total sample) receiving atypicals as compared with the poor adherence group (25%). The improved tolerability claimed for atypical antipsychotics, particularly the lower liability for extrapyramidal symptoms, might well promote better adherence in those cases where adverse side effects have played a mediating role in poor adherence (51). Thus, the use of atypical antipsychotics in our sample may have rendered a link between adverse side effects and adherence less critical.

These findings prompt further speculation on how attitudes may interact with side effects and adherence. Patients who view treatment as ineffective or unnecessary may be relatively intolerant of adverse side effects, which could reinforce their reluctance to take medication. By contrast, where patients are adherent with medication, it may be because they acknowledge both the direct and indirect benefits of medication despite the presence of adverse side effects. Thus, the relationship between adverse side effects and adherence may not be as straightforward as it first appears.

Adherence and subjective response

In this study, subjective well-being as measured by the SWN was not a significant explanatory variable of adherence behaviour at treatment inception. This finding is at variance with some previous studies of the clinical impact of the adverse subjective experience of antipsychotic medication (45, 47). One explanation for this discrepancy might be that subjective well-being is a more potent influence on adherence during maintenance treatment than the early, acute phase of treatment. However, as discussed above, the better tolerability and reduced side effect burden of atypical drugs as compared with conventional antipsychotics may also be relevant. For example, Naber and colleagues (52) reported an improved sense of well-being and better adherence in patients switched from conventional antipsychotics to clozapine.

Along the lines already argued above, a further explanation relates to the short duration of antipsychotic treatment in the patients in this study sample. The extent to which they could be expected to reliably attribute any subjective feelings of well-being or dysphoria to either their illness or medication must be open to question. Certainly, the difficulties in differentiating objectively between antipsychotic side effects and aspects of psychopathology, for example, drug-induced bradykinesia and both negative and depressive symptoms, have been previously highlighted (53).

Adherence and substance misuse

Findings in relation to adherence and alcohol and non-alcohol use have been inconsistent. Some studies in patients with chronic schizophrenia have found a significant association (54, 55) but not all (56). Similarly, while some prospective studies of patients with first-episode psychosis have identified substance use as a predictor of poor adherence (5, 10) others have not (9). In the present study, there was no association between reported lifetime use of alcohol or non-alcohol substances and compliance with medication.

The measurement of adherence

Our use of an observer rated measurement of adherence, the CRS, raises methodological issues. The validity of such an indirect measure could be challenged although all the available methods of adherence measurement have their own limitations as described by Kemp and colleagues (13). These authors used the same measure of adherence as our study and found that adherence strongly correlated with Drug Attitude Inventory (DAI), a measure known to be predictive of medication adherence. In our study, adherence correlated strongly with the ROMI, also a measure known to be predictive of medication adherence (19). These findings therefore lend concurrent validity to our measure of adherence.

Findings from this study of first-episode patients may not generalize to people with schizophrenia at later stages. Factors that mediate adherence during the maintenance phase of treatment may be different to those of the acute phase. Nevertheless, the findings may point to factors relevant to any adherence-enhancing interventions embarked upon during the early stages of the illness.

Acknowledgement

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