

Compliance in Schizophrenia: Psychopathology, Side Effects, and Patients' Attitudes Toward the Illness and Medication

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Objective: In a cross-sectional study, we investigated the influence of several factors on compliance in schizophrenia outpatients, including patients' attitudes toward the illness and medication, specifically antipsychotic medication; adverse effects; and attitudes of caregivers and relatives toward the illness and medication.

Method: Patients suffering from schizophrenia (ICD-10 diagnosis) of at least 1-year's duration whose discharge from an inpatient ward was at least 6 weeks prior to inclusion in the study were investigated. Study instruments included a semi-structured compliance interview, the Positive and Negative Syndrome Scale, the Udvalg for Kliniske Undersogelser Side Effect Rating Scale, the St. Hans Rating Scale, and the Hillside Akathisia Scale. Data were collected from May 1998 to December 2001.

Results: 52.5% (N = 32) of the 61 investigated patients were fully compliant, 39.3% (N = 24) were partially compliant, and only 8.2% (N = 5) were noncompliant. We found positive correlations between compliance and the patients' feelings of a positive effect of the drug on the illness, between compliance and negative symptoms, and between compliance and antipsychotic-induced psychological side effects.

Conclusion: Our findings reemphasize the importance of taking subjective attitudes and concerns of patients with respect to their illness and medication seriously. Therefore, it is indispensable to include patients and, if possible, their relatives in the treatment decision process to enhance medication compliance in schizophrenia patients.

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Although there is overwhelming evidence that antipsychotics are effective in reducing relapse rates among patients with schizophrenia, up to 50% of first-episode patients relapse during the first year of illness when treated in everyday clinical practice.¹ Controlled clinical trials, on the other hand, found a relapse rate of only 20%.² One reason for this discrepancy may be non-compliance. Only about one third of patients suffering from a schizophrenic disorder are reported to be fully compliant. Another one third are said to be partially compliant, meaning that these patients will either reduce the dose of the drug prescribed or fail to take medication from time to time. The remaining patients do not follow prescription instructions at all.^{3,4}

Generally, compliance can be seen as an indicator of quality and effectiveness of communication between doctor and patient. Therefore, compliance should not be seen as a 1-way process, but as a result of complex factors influencing the patient's willingness to follow prescription recommendations given by the treating physician.⁵ A number of factors appear to influence drug compliance in patients with schizophrenia, including the patient's attitude toward the illness itself and the medication,⁶⁻¹² as well as the function of caregivers and relatives in motivating the patient to take drugs as prescribed.¹³

Next to those influences, antipsychotic-induced adverse effects, especially extrapyramidal side effects (EPS), sexual disturbances, and weight gain, are generally stated to be of importance in the context of noncompliance.¹⁴⁻¹⁸ When the available literature is carefully studied, it is interesting to note that not all studies have found clear correlations between adverse events and noncompliance. There are a number of studies that failed to find a negative influence of adverse events on compliance.^{5,17,19} Furthermore, psychopathologic symptoms are of relevance regarding compliance. Miner and Rosenthal,²⁰ for instance, found that patients with the more negative symptoms were better compliers with respect to attending outpatient appointments, whereas those with mixed syndromes were most likely to be noncompliant.

The purpose of this study was to investigate the influence of the previously mentioned factors on drug com-

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pliance in outpatients with schizophrenia. In particular, we studied the following 4 questions: (1) Is compliance affected by the patient's attitude toward the illness and medication? (2) Is compliance influenced by caregivers and/or relatives inquiring about drug intake? (3) Is compliance related to the patient's psychopathology? and (4) Is compliance affected by antipsychotic-induced side effects?

METHOD

We studied 61 patients who had fulfilled clinical ICD-10 criteria for schizophrenia for at least 1 year and who had been discharged from an inpatient ward at least 6 weeks before inclusion in the study. All patients were regular voluntary attenders of our schizophrenia outpatient clinic (Innsbruck, Austria). Patients gave written consent prior to participation in the study. Data were collected from May 1998 to December 2001.

To assess psychopathologic symptoms of schizophrenia, we used the Positive and Negative Syndrome Scale (PANSS).²¹ To quantify side effects, we used the Udvalg for Kliniske Undersøgelser Side Effect Rating Scale (UKU).²² The St. Hans Rating Scale²³ and the Hillside Akathisia Scale (HAS)²⁴ were used to rate EPS.

The UKU comprises a total of 48 symptoms divided into 4 groups: psychological (e.g., concentration disturbances, loss of energy, loss of memory, depression, inner unrest, increase of sleeping duration, reduction of sleeping duration, increased dream activity, emotional indifference), neurologic (e.g., extrapyramidal symptoms, epileptic seizures, paresthesia), autonomic (e.g., accommodation disturbances, increased salivation, reduced salivation, nausea/vomiting, diarrhea, constipation, micturition disturbances, polyuria/polydipsia, orthostatic dizziness, palpitations/tachycardia, increased tendency to sweating), and others (e.g., skin disturbances, weight changes, disturbances of the menstrual cycle, sexual disturbances, headaches, physical or psychological dependence). Each symptom is scored on a severity scale from 0–3. The St. Hans Rating Scale consists of 4 subscales: an akathisia subscale, a dystonia subscale, a parkinsonian symptom subscale, and a dyskinesia subscale, scored from 0 = absent to 6 = severe. The HAS consists of a subjective and an objective subscale assessing 1 resting and 2 challenge conditions scored from 0 = absent to 4 = present and not controllable, and an item for the global assessment of akathisia (0 = no akathisia to 7 = worst akathisia).

To assess compliance itself and several factors influencing compliance, we used a semistructured self-reporting compliance interview (Appendix 1) that covers the following issues: patients' personal and clinical data, type and dose of medication, patients' attitudes toward their illness in comparison with other serious diseases, and questions regarding who asks the patient about taking medication and about the reasons for drug intake failure.

Furthermore, questions about the attitude toward antipsychotics and medication in general as well as questions about the possible reactions of relatives and professional caregivers toward noncompliance are also included. Most questions can be answered by either "yes," "no," or "don't know," or "more," "equally," "less serious," or "don't know." Three questions must be answered in a narrative fashion.

Compliance was defined by the following: (1) fully compliant = medication never missed, (2) partially compliant = missed medication for a maximum of 7 consecutive days or nonauthorized dose reduction during the last 3 months, and (3) noncompliant = missed medication for more than 7 consecutive days during the last 3 months. To objectify compliance, we also measured plasma levels of the antipsychotics used 12 hours after last intake of medication. Plasma levels were quantified by tandem mass spectrometry on a Micromass Quattro Ultima (Manchester, United Kingdom).

Data Analysis and Statistical Methods

The 4 main questions of this study were analyzed by comparing compliant patients (including those who were partially compliant) and noncompliant patients with respect to the following criteria. To measure attitudes toward medication (question 1), the questionnaire items about reasons for taking medication were combined to form 3 subscales: positive effect on illness, positive effect on everyday life, and satisfying other people (each with a range from 0 = complete disagreement to 100 = complete agreement). Caregivers or relatives inquiring about drug intake (question 2) were evaluated by the questionnaire item "Who asks most often whether you take your medication?" Psychopathology (question 3) was measured by the 3 subscales of the PANSS scale, and drug side effects (question 4) were summarized using the subscores of the UKU, i.e., total number of psychological, neurologic, autonomic, and other side effects. A side effect on the UKU was considered as present if its rating was ≥ 1 .

The Mann-Whitney U test was used to compare compliant and noncompliant patients with respect to ordinal scaled variables or subscales (e.g., subscores of the PANSS). Fisher exact test was employed for group comparisons involving dichotomous variables, e.g., dichotomized side effect ratings, and the χ^2 test was used for group comparisons involving other categorical variables. To assess the relationship between the degree of compliance (non, partially, and fully) and the subscales investigated, we supplemented the analyses by ordinal regression analysis with degree of compliance as the dependent variable, considering the independent variables one by one.²⁵

In addition to the previously mentioned univariate analyses, a logistic regression analysis was performed to assess the joint effect of psychopathology, side effects, attitudes, and other persons' influence on compliance. The

Table 1. Sociodemographic and Clinical Variables of 61 Patients With Schizophrenia

Variable	Patients
Age, mean $\pm$ SD, y	35.2 $\pm$ 8.7
Sex, N (%)	
Male	41 (67)
Female	20 (33)
Duration of illness, mean $\pm$ SD, y	9.6 $\pm$ 8.5
PANSS, mean $\pm$ SD score	
Positive	10.6 $\pm$ 3.9
Negative	14.6 $\pm$ 6.4
Total	50.3 $\pm$ 14.6
Medication, N (mean $\pm$ SD dose)	
Fluphenazine	2 (50 $\pm$ 0 mg/2 wk)
Flupenthixol	1 (40 $\pm$ 0 mg/4 wk)
Haloperidol	7 (39 $\pm$ 47.1 mg/4 wk)
Clozapine	22 (267 $\pm$ 121.4 mg/d)
Zotepine	4 (193.7 $\pm$ 71.8 mg/d)
Risperidone	5 (3.6 $\pm$ 0.89 mg/d)
Sertindole	2 (10 $\pm$ 2.82 mg/d)
Olanzapine	18 (11.5 $\pm$ 5.72 mg/d)

effect of these variables on degree of compliance was analyzed using ordinal regression.

RESULTS

Demographic data as well as percentage of compliant, partially compliant, and noncompliant patients are shown in Table 1. All patients attended a specialized outpatient clinic for schizophrenia. This clinic is characterized by continuity of care, meaning that the doctor responsible for the outpatient setting builds a rapport with the patients while they are inpatients. After discharge, the patient is seen regularly by the same doctor and nonmedical professionals.

All patients approached agreed to participate. Of the 61 patients included in the study, 52.5% (N = 32) were fully compliant, 39.3% (N = 24) were partially compliant, and only 8.2% (N = 5) were noncompliant according to their self-reports. Plasma drug levels corresponded with subjective compliance in 87.2% of cases. Eight patients (13.1%) reported being either fully or partially compliant despite nondetectable levels of the respective antipsychotic. Although there was good accordance between subjective reports on compliance and plasma drug levels, we refrained from adding plasma levels into the statistical analysis because plasma levels were only available for 77% of the patients.

Influence of Patients' Attitudes Toward Medication on Compliance

Compliant and partially compliant patients reported positive effects on their illness as being a reason for taking medication more often than noncompliant patients (mean score = 88.0 vs. 65.0 on a 0–100 scale). Although this difference was only significant at a trend level ($p = .093$, Mann-Whitney U test), the result was confirmed by

a significant association between the degree of compliance (non-, partially, fully compliant) and the “positive effects on illness” subscale ($p = .007$, ordinal regression). Moreover, compliant and partially compliant patients indicated positive effects of medication on everyday life (mean score = 68.0) more frequently when compared with noncompliant patients (mean score = 42.5). Again, this difference failed to reach statistical significance ($p = .072$, Mann-Whitney U test), but the association between degree of compliance and this variable was significant ($p = .043$) (Table 2).

Influence of Clinicians and Significant Others Inquiring About Drug Intake on Compliance

The subgroup of compliant and partially compliant patients differed significantly from the noncompliant patients regarding the person (psychiatrist, relatives, others/nobody) inquiring most frequently about drug intake ($\chi^2 = 9.31$, $df = 2$, $p = .010$). Post hoc analyses revealed that compliant and partially compliant patients were asked about drug intake most frequently by their psychiatrists (41% [23/56]), while none of the noncompliant patients reported this ($p = .074$, Fisher exact test); conversely, a higher proportion of noncompliant patients (60% [3/5]) than compliant or partially compliant patients (8.9% [5/56]) stated that their relatives inquire most often about their drug intake ($p = .014$). A considerable percentage of patients were not asked by anyone (25.5% of compliant and partially compliant patients and 20% of noncompliant patients) (Table 2).

Relationship Between Psychopathology and Compliance

We found that compliant and partially compliant patients showed significantly more negative symptoms than noncompliant patients (mean PANSS negative score = 15.1 vs. 9.8; $p = .044$). We found no statistical association between compliance and positive symptoms. PANSS total scores were higher in compliant and partially compliant patients than in noncompliant patients (mean PANSS total score = 51.4 vs. 39.2; $p = .030$). When considering compliance as an ordered categorical variable (degree of compliance), an association with the negative symptoms score was found at a trend level ($p = .087$), while none of the other PANSS scores were significantly related to the degree of compliance.

Relationship Between Side Effects and Compliance

With respect to EPS (Table 3), no statistically significant relationship between compliance and side effects as assessed by the UKU was observed. However, we found a significant association between the total number of psychological side effects (assessed by the UKU) and compliance: compliant and partially compliant patients showed a mean total number of 3.9 side effects, whereas

Table 2. Relationship Between Patients' Attitudes Toward Medication, Inquiry About Medication Intake, Psychopathology, Side Effects, and Compliance^a

Variable	Compliant Patients (N = 32)	Partially Compliant Patients (N = 24)	Noncompliant Patients (N = 5)	Noncompliant Patients vs. All Others ^{c,d}	Linear Trend ^{d,e}
Reasons for taking medication (score 0–100)					
Positive effect on illness	92.2 ± 22.3	82.6 ± 25.5	65.0 ± 41.8	p = .093*	p = .007
Positive effect on everyday life	72.4 ± 29.2	62.5 ± 30.8	42.5 ± 30.1	p = .072*	p = .043
Satisfy other people	68.1 ± 38.3	57.6 ± 43.6	60.0 ± 41.8	NS	
Inquiry about medication intake (who asks most often?)					
Psychiatrist, N (%)	14 (44)	9 (38)	0 (0)	p = .074*	NS
Relatives, N (%)	3 (9)	2 (8)	3 (60)	p = .014	NS
Other, N (%) ^b	15 (47)	13 (54)	2 (40)	NS	NS
Psychopathology (PANSS)					
Positive	10.4 ± 3.8	11.0 ± 3.9	9.8 ± 5.2	NS	NS
Negative	15.6 ± 6.6	14.2 ± 5.9	9.8 ± 5.1	p = .044	p = .087*
Total	52.1 ± 14.3	50.3 ± 14.3	39.2 ± 15.0	p = .030	NS
Side effects (UKU)					
Psychological	3.5 ± 2.3	4.5 ± 2.0	0.8 ± 1.8	p = .004	NS
Neurologic	0.9 ± 1.0	1.0 ± 1.4	0.4 ± 0.9	NS	NS
Autonomic	1.0 ± 2.1	0.9 ± 1.6	0.4 ± 0.5	NS	NS
Others	1.2 ± 1.5	1.4 ± 1.4	0.4 ± 0.5	NS	NS

^aAll values are mean ± SD unless otherwise stated.^bPatients who were not asked by anyone are included in the category "other."^cStatistical evaluation by Mann-Whitney U test for the variables "reasons for taking medication," "psychopathology," and "side effects" and by Fisher exact test for the variable "inquiry about medication intake."^dNS = p > .1.^eCompliance is considered as an ordered categorical variable (statistical evaluation by Spearman rank correlation coefficient).

*p < .1, but p > .05.

Abbreviations: NS = not significant, PANSS = Positive and Negative Syndrome Scale, UKU = Udvalg for Kliniske Undersøgelser Side Effect Rating Scale.

Table 3. Extrapyramidal Motor Side Effects (UKU) in Relation to Compliance Among Patients With Schizophrenia^{a,b,c}

Side Effect	Fully/Partially Compliant (N = 56) % (N)	Noncompliant (N = 5) % (N)
Dystonia	11 (6)	0
Rigidity	13 (7)	0
Hypokinesia/akinesia	25 (14)	20 (1)
Tremor	6 (3 of 54)	0
Hyperkinesia	15 (8 of 55)	20 (1)
Akathisia	19 (10 of 54)	0

^aAll side effects with a score ≥ 1 on the UKU.^bNo statistically significant differences between the 2 groups for any of the side effects (p > .1, Fisher exact test).^cSome patients experienced more than 1 side effect.

Abbreviation: UKU = Udvalg for Kliniske Undersøgelser Side Effect Rating Scale.

noncompliant patients had a mean of only 0.8 of these adverse events (p = .004). There was no significant association between compliance and the total number of neurologic, autonomic, or "other" side effects listed on the UKU. The analysis of the St. Hans and HAS scores did not add additional insight into the findings derived from the UKU, which also covers EPS. They are therefore not presented here in the interest of space and readability.

In a logistic regression analysis performed to find out which of the variables studied best predicts compliance (full/partial compliance vs. noncompliance), 3 variables remained in the model ($\chi^2 = 22.69$, df = 3, p < .0001)

as statistically significant predictors: "positive effect on everyday life" as a reason for taking drugs ($\chi^2 = 6.59$, df = 1, p = .010), psychiatrists inquiring about drug intake ($\chi^2 = 10.56$, df = 1, p = .001), and a higher total number of psychological side effects ($\chi^2 = 13.52$, df = 1, p < .001). The subscales of the PANSS did not contribute significantly to the patients' compliance after adjustment for the other variables. The corresponding analysis with "degree of compliance" as the dependent variable (ordinal regression) yielded only 1 significant predictor (positive effect of drugs on illness, $\chi^2 = 5.17$, df = 1, p = .023) and a less pronounced overall significance of the model (p = .023 in comparison with p < .0001).

DISCUSSION

Obviously, the compliance rate in our study is high compared with that of other reports.³ Clearly, our results would have been strengthened by using the information derived from plasma drug level measurements to validate subjective reports on compliance behavior. This measurement was originally planned but not possible for various reasons, most importantly because some patients refused to have blood drawn.

That we studied regular outpatient clinic attenders, a group compliant per definition, may account for the high compliance rate in our study. This fact also implies that the relevance of our results may be restricted to an at least

superficially compliant population, as noncompliers are usually not available for such interviews. The percentage of male patients (60%) reflects the sex relation of the attenders of our clinic. More male patients contact this clinic; one reason might be better social functioning of females as compared with males suffering from schizophrenia.²⁶ This difference in functioning should also be discussed relative to the observation that females generally show better compliance than males.²⁷ That we investigated a relatively healthy population, which is reflected by a low PANSS total score, also raises some concerns with regard to generalizability of our results. Compliance of patients with worse psychopathology, specifically inpatients, may follow different patterns that need to be studied separately.

We found that subjectively experienced positive effects of drugs correlated significantly with compliance. Several previous studies^{13,28} also showed a clear correlation between subjective experiences and compliance. Correspondingly, one of the reasons for noncompliance may be the belief that medication is not effective. It is therefore essential to pay attention to the patient's subjective perception of the effects of drugs. If this aspect is neglected, patient compliance is at risk. Especially during long-term treatment, the patient's attitude toward antipsychotic medication and perspective regarding subjective well-being and quality of life are of major relevance. Therefore, a continuous benefit/risk discussion needs to be held with the patient.

Furthermore, reliable information plays an important role in the doctor/patient relationship. It has been shown in various studies^{19,29,30} that a working therapeutic alliance is of particular significance regarding compliance. We found that the subgroup of compliant and partially compliant patients were asked more often by significant others about drug intake than were noncompliant patients. Even though the number of noncompliant patients is very small, this finding warrants at least some consideration about the supportive function of doctors and relatives with respect to motivation for medication intake. To investigate the influence of the patients' relatives toward medication and illness, we originally tried to investigate those persons as well but failed because the majority of patients refused to involve their relatives in the study.

The fact that we found less compliance with a decrease in PANSS total scores may be seen in the context of healthier patients demonstrating less subjective need to continue taking medication. This finding emphasizes the importance of encouraging patients who are in remission to continue treatment in order to prevent relapse. Our finding that compliant patients had significantly more negative symptoms confirms the findings of Miner and Rosenthal,²⁰ although different study outcome measures (attending appointments in Miner and Rosenthal's study vs. compliance with medication in ours) render a comparison of the two studies difficult. Our findings also need to be discussed

in the light of conflicting results reported by Tattan and Creed,³¹ who found a positive correlation between negative symptoms and noncompliance. This discrepancy might be accounted for by sampling differences, as all patients included in the investigation by Tattan and Creed received depot neuroleptics, whereas 85% of our patients (N = 52) were treated with oral second-generation antipsychotics.

As traditional neuroleptics have a higher likelihood to induce EPS,^{32,33} including akinesia, which is difficult to differentiate from primary negative symptoms, one may speculate that distressing motor side effects, sometimes referred to as secondary negative symptoms, have contributed to the compliance problems reported by Tattan and Creed.³¹ Furthermore, compliance was measured by the patients actually "showing up" to receive their depot medications in the study by Tattan and Creed, which means that those patients were definitely compliant, whereas we used a self-reported compliance interview. In addition, patients who are taking depot medication usually represent a more difficult-to-treat population than patients taking oral medication. Considering all of these arguments, it is likely that the discordant results of our study and those of Tattan and Creed are due to a discrepant methodology and sample selection.

We found more side effects in the group of compliant and partially compliant patients. This seemingly paradoxical result can be explained by the higher risk to develop side effects in patients who actually take their drugs. On the other hand, it must be seen in the context of the special treatment setting of the patient group we investigated. Almost all of the patients allocated to this study participated in a drug monitoring program that enhances the likelihood to detect side effects at a very early stage and offers the possibility to react quickly. Adjustments can be made by reducing the dose, adding specific comedication, or switching to another antipsychotic. In other instances in which a tolerance to adverse events is to be expected, patients are supported in "sitting out" side effects until they remit spontaneously. It is possible to minimize the negative impact of side effects on compliance by using such an early detection and intervention strategy. Next to that, such a strategy can be expected to improve the therapeutic alliance, a cornerstone of schizophrenia treatment and compliance. In addition, it can be conceived that patients with side effects are monitored more closely, thereby enhancing compliance. These findings also corroborate another study by our group,³⁴ showing that side effects do not correlate negatively with compliance.

Furthermore, we found a significant positive correlation between psychological side effects and compliance. As psychological side effects include concentration disturbances, loss of energy, loss of memory, and emotional indifference, it is difficult to draw the fine line between these phenomena and negative symptoms. Therefore, this result

could be interpreted along the same lines as the relationship between compliance and negative symptoms.

When we took a multivariate approach, we found that patients' positive attitudes toward medication, a good doctor-patient relationship, and psychological side effects turned out to be significant predictors of patient compliance in our study, whereas psychopathology was no longer found to be of major relevance once the influence of the other 3 factors had been accounted for. Closer inspection of the data revealed a rather strong correlation between psychopathologic symptoms and the psychological side effects subscale of the UKU ($r = 0.51$, Spearman correlation with PANSS total score). The fact that side effects were retained in the list of significant predictors of patient compliance while psychopathology was excluded should therefore not be overinterpreted.

Considering the wide range of drug adherence patterns in patients, we defined 3 levels of compliance: full, partial, and noncompliance. Regarding the aspects investigated in this study, our results suggest a clearer distinction between noncompliant patients and at least partially compliant patients than between fully compliant and not fully compliant patients. In fact, compliant patients and those defined as partially compliant showed very similar values both in the PANSS subscales and in the UKU side effect scores and only small and insignificant differences regarding their attitudes toward antipsychotic medication. Non-compliant patients, however, differed from the 2 other patient groups in several respects as discussed previously. Because the number of noncompliant patients was low in this study, further research with larger samples of non-compliant patients would be required to confirm their observed characteristics.

In conclusion, our findings reemphasize the importance of taking subjective attitudes and concerns of patients seriously and including patients, and if possible, their significant others, into the treatment decision process.

Drug names: clozapine (Fazaclo, Clozaril, and others), fluphenazine (Prolixin, Permitil, and others), haloperidol (Haldol and others), olanzapine (Zyprexa and others), risperidone (Risperdal).

REFERENCES

- Gaebel W, Pietzker A. One year outcome of schizophrenic patients: the interaction of chronicity and neuroleptic treatment. *Pharmacopsychiatry* 1985;18:235-239
- Kissling W. Guidelines for Neuroleptic Relapse Prevention in Schizophrenia. Brugge, Belgium: Springer-Verlag; 1989:1-5
- Blackwell B. Treatment adherence. *Br J Psychiatry* 1976;129:513-531
- Wright EC. Non-compliance or how many aunts has Mathilda? *Lancet* 1993;342:909-913
- Fleischhacker WW, Meise U, Günther V, et al. Compliance with antipsychotic drug treatment: influence of side effects. *Acta Psychiatr Scand* 1994;89(suppl 383):11-15
- van Putten T, May PRA, Marder SR. Subjective response to thiothixene and chlorpromazine. *Psychopharmacol Bull* 1980;16:36-38
- Hogan TP, Awad AG, Eastwood MR. Early subjective response and prediction of outcome to neuroleptic drug therapy in schizophrenia. *Can J Psychiatry* 1985;30:246-248
- Awad AG. Drug therapy in schizophrenia: variability of outcome and prediction of response. *Can J Psychiatry* 1989;34:711-720
- Collins EJ, Hogan TP, Desai H. Measurement of therapeutic response in schizophrenia: a critical survey. *Schizophr Res* 1991;5:249-253
- Awad AG. Quality of life of schizophrenic patients on medication: an implication for new drug trials. *Hosp Community Psychiatry* 1992;43:262-265
- Awad AG. Subjective response to neuroleptics in schizophrenia. *Schizophr Bull* 1993;19:606-618
- Lewander T. Neuroleptics and neuroleptic-induced deficient syndrome. *Acta Psychiatr Scand* 1994;89(suppl 380):8-13
- Fenton WS, Blyler CR, Heinssen RK. Determinants of medication compliance in schizophrenia: empirical and clinical findings. *Schizophr Bull* 1997;23:637-651
- Young JL, Zolana HV, Shepler L. Medication non-compliance in schizophrenia: codification and update. *Bull Am Acad Psychiatry Law* 1986;14:105-122
- Silverstone T, Smith G, Goodall E. Prevalence of obesity in patients receiving depot antipsychotics. *Br J Psychiatry* 1988;153:214-217
- Pfeifer W, Kockott G, Fischl B, et al. Unerwünschte Wirkungen psychopharmakologischer Langzeittherapie auf die sexuellen Funktionen. *Psychiatr Prax* 1991;18:92-98
- Buchanan A. A two-year prospective study of treatment compliance in patients with schizophrenia. *Psychol Med* 1992;22:787-797
- Hummer M, Fleischhacker WW. Non-motor side effects of novel antipsychotics. *Curr Opin CPNS Investigational Drugs* 2000;2:45-51
- Linden M. Therapeutische Ansätze zur Verbesserung von Compliance. *Nervenarzt* 1979;50:109-114
- Miner CR, Rosenthal RN. Prediction of compliance with outpatient referral in patients with schizophrenia and psychoactive substance use disorders. *Arch Gen Psychiatry* 1997;54:706-712
- Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13:261-276
- Lingjaerde O, Ahlfors UG, Bech P, et al. The UKU Side Effect Rating Scale: A New Comprehensive Rating Scale for Psychotropic Drugs and a Cross Sectional Study of Side Effects in Neuroleptic-Treated Patients. *Acta Psychiatr Scand* 1987;76(suppl 334):1-100
- Gerlach J, Korgaard S, Clemmesen P, et al. The St. Hans Rating Scale for Extrapyramidal Side Effects: reliability and validity. *Acta Psychiatr Scand* 1993;87:244-252
- Fleischhacker WW, Bergmann KJ, Perovich R, et al. The Hillside Akathisia Scale: a new rating instrument for neuroleptic-induced akathisia. *Psychopharmacol Bull* 1989;25:222-226
- McCullagh P, Nelder JA. Generalized Linear Models. London, England: Chapman and Hall; 1983
- Leung A, Chue P. Sex differences in schizophrenia, a review of the literature. *Acta Psychiatr Scand* 2000;101:3-38
- Farina A. Are women nicer people than men? sex and the stigma of mental disorders. *Clin Psychol Rev* 1981;1:223-243
- Ruscher SM, de Wit R, Mazmanian D. Psychiatric patient's attitudes about medication and factors affecting non-compliance. *Psychiatr Serv* 1997;48:82-85
- Meise U, Günther V, Gritsch S. Die Bedeutung der Arzt-Patienten-Beziehung für die Patienten-Compliance. *Wien Klin Wochenschr* 1992;104:267-271
- Ley P, Spielman MS. Communication in an outpatient setting. *Br J Soc Clin Psychol* 1965;4:114-116
- Tattan TM, Creed FH. Negative symptoms of schizophrenic patients and compliance with medication. *Schizophr Bull* 2001;27:149-155
- Leucht S, Pitschel-Walz G, Abraham D, et al. Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone and sertindole compared to conventional antipsychotics and placebo: a meta-analysis of randomized controlled trials. *Schizophr Res* 1999;35:51-68
- Fleischhacker WW, Hummer M. Drug treatment of schizophrenia in the 1990s: achievements and future possibilities in optimising outcomes. *Drugs* 1997;53:915-929
- Hummer M, Kemmler G, Kurz M, et al. Sexual disturbances during clozapine and haloperidol treatment for schizophrenia. *Am J Psychiatry* 1999;156:631-633
- Rettenbacher MA, Burns T, Kemmler G, et al. Schizophrenia: attitudes of patients and professional carers towards the illness and antipsychotic medication. *Pharmacopsychiatry* 2004;37:103-109

Appendix 1. Adherence to Medication Regimens^a

1. What is the name of your medication? _____				
2. What is the prescribed dose? _____				
3. How are you supposed to take it? _____				
4. a) If you have been taking oral medication during the last 3 months, what was the longest period you remained without medication?	☐ None	☐ Less than 1 day	☐ 1–7 days	☐ More than 7 days
b) If you were receiving a depot during the last 3 months, what was the longest delay you experienced in receiving your injection (counting from the date your depot was due?)	☐ None	☐ 1–3 days	☐ More than 3 days	
		Yes	No	Don't Know
5. Overall, has your medication been useful to you?	☐	☐	☐	☐
6. Would you recommend your medication to someone who was suffering from schizophrenia?	☐	☐	☐	☐
7. Do you prefer:				
a) oral medication rather than depot injection?	☐	☐	☐	☐
b) depot injection rather than oral medication?	☐	☐	☐	☐
8. Have you tried both?	☐	☐	☐	☐
	More	Equally	Less Serious	Don't Know
9. Suffering from schizophrenia is more/equally/less serious than suffering from	☐	☐	☐	☐
a) High blood pressure	☐	☐	☐	☐
b) Diabetes	☐	☐	☐	☐
c) Epilepsy	☐	☐	☐	☐
d) Cancer	☐	☐	☐	☐
e) Depression	☐	☐	☐	☐
f) Rheumatoid arthritis	☐	☐	☐	☐
10. From the following list:				
A. General practitioner	D. Intensive outreach worker	G. Hostel staff	J. My friends	
B. Psychiatrist	E. Psychologist	H. My partner	K. Patients	
C. Community psychiatric nurse	F. Social worker	I. My relatives	L. Patients on the same medication	
(Please give the corresponding capital letter of the alphabet from the above list in answering the following questions.)				
a) Who frequently asks whether you take your medication? (list all who frequently ask)				
b) Who more frequently asks whether you take your medication? (list 3 at the most)				
c) Whose advice to take your medication are you more likely to follow? (list 3 at the most)				
d) Who gives you advice NOT to take your medication? (List all who give that advice)				
e) Whose advice NOT to take your medication are you more likely to follow? (List 2 at the most)				
		Yes	No	Don't Know
11. When I do not take my medication, usually there is a reason explaining why not?	☐	☐	☐	☐
12. When I stop taking my medication, mental health professionals could help me to restart it?	☐	☐	☐	☐
13. Are there any benefits from taking medication for schizophrenia?	☐	☐	☐	☐
14. Regarding maintenance medication for schizophrenia, I believe that:				
a) It controls the illness	☐	☐	☐	☐
b) It prevents relapses	☐	☐	☐	☐
c) It helps me enjoy life more	☐	☐	☐	☐
d) It helps me feel better	☐	☐	☐	☐
e) It helps me cope better	☐	☐	☐	☐
f) It gives me more energy	☐	☐	☐	☐
g) By taking it, I keep my doctor/community psychiatric nurse satisfied	☐	☐	☐	☐
h) By taking it, I keep my relatives satisfied	☐	☐	☐	☐
15. Which 3 of the above are the most important for you? (Please give the corresponding letter of the alphabet only)				
1. _____ 2. _____ 3. _____				
16. Are there any problems from taking medication for schizophrenia?	☐	☐	☐	☐

continued

Appendix 1. Adherence to Medication Regimens (cont.)

	Yes	No	Don't Know
17. Regarding maintenance medication for schizophrenia, I believe that			
a) It cannot control the illness	☐	☐	☐
b) It cannot prevent relapses	☐	☐	☐
c) It makes it difficult for me to enjoy life	☐	☐	☐
d) It makes me feel unwell	☐	☐	☐
e) It makes it difficult for me to cope	☐	☐	☐
f) It makes me tired	☐	☐	☐
g) It is expensive	☐	☐	☐
h) It has side effects	☐	☐	☐
i) Oral medication tastes awful	☐	☐	☐
j) It is embarrassing to have depot injections	☐	☐	☐
k) When I get better, people have more demands on me	☐	☐	☐
18. Which 3 of the above are the most important for you? (Please give the corresponding letter of the alphabet only)			
1. _____ 2. _____ 3. _____			
19. Maintenance medication for schizophrenia			
a) Is useful only when someone is very ill	☐	☐	☐
b) Is useful only if you believe that it will work	☐	☐	☐
20. Keeping myself in good mental health is important	☐	☐	☐
21. If you suffer from schizophrenia, medication is helpful in keeping you in good mental health	☐	☐	☐
22. Suffering from schizophrenia carries a stigma	☐	☐	☐
23. Taking medication for schizophrenia carries a stigma on its own	☐	☐	☐
24. I have been so ill that:			
a) I could not realize I needed help to get better	☐	☐	☐
b) I could not realize I needed medication	☐	☐	☐
25. A treatment should lead to a cure with no need for further treatment	☐	☐	☐
26. When I do not take my medication for schizophrenia, my doctor/community psychiatric nurse:			
a) Are concerned	☐	☐	☐
b) Feel frustrated	☐	☐	☐
c) Are critical of me	☐	☐	☐
d) Care less about me	☐	☐	☐
e) Are helping me less	☐	☐	☐
27. When I do not take my medication for schizophrenia, my relatives:			
a) Are concerned	☐	☐	☐
b) Feel frustrated	☐	☐	☐
c) Are critical of me	☐	☐	☐
d) Care less about me	☐	☐	☐
e) Are helping me less	☐	☐	☐
28. When I am unhappy with my doctor/community psychiatric nurse, it happens that I do not take my medication	☐	☐	☐
29. When I am unhappy with my relatives, it happens that I do not take my medication	☐	☐	☐
30. When seen by a mental health professional:			
a) I should be asked whether I take my medication as prescribed	☐	☐	☐
b) I am frequently asked whether I take my medication as prescribed	☐	☐	☐
c) It is offensive for them to ask whether I take my medication as prescribed	☐	☐	☐
31. If a relative of mine was suffering from schizophrenia and not taking his/her medication as prescribed:			
a) I would try and find out why he/she is not taking it	☐	☐	☐
b) I would do everything I could to get them to take it	☐	☐	☐
32. The following can be useful for helping me to take my medication as prescribed:			
a) Giving me praise when I take it as prescribed	☐	☐	☐
b) Giving me money when I take it as prescribed	☐	☐	☐
c) Offering me free lunches when I take it as prescribed	☐	☐	☐
d) Warning me about the consequences of not taking it as prescribed	☐	☐	☐
e) Showing to me the course of my illness during a relapse, as described in my hospital medical notes	☐	☐	☐
33. Is there anything else that can be useful in helping you take your medication as prescribed?	☐	☐	☐
34. What? (Could you elaborate in the following space?)			

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