PSYCHOPHARMACOTHERAPY

4.3. Nonadherence to antipsychotic treatment in patients with schizophrenic disorders

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Summary

Adherence to treatment is a general indicator of quality and success of communication between the physician and the patient. It means the extent to which patient behaviour, in terms of taking medications, following diets, or executing life-style changes, coincides with medical or health advice. Nonadherence to antipsychotic therapy in patients with schizophrenia is far more widespread than clinicians assume. Lower nonadherence in therapy based on antipsychotics of the second generation compared with conventional medications has already been indicated by early reports. The consequences of nonadherence include exacerbation of symptoms, an increased relapse rate, psychiatric hospitalization hospitalisation, and less favourable patient prognosis. There are several factors that cause treatment nonadherence in schizophrenia: causes derived from the schizophrenic disorder itself, patient characteristics, causes associeted associated with the health-care system, and the antipsychotic treatment itself.

4.3.1. Introduction

Antipsychotic treatment represents the basis of comprehensive therapy of schizophrenic disorders; it consists of managing acute psychotic symptoms, of continuation treatment, and long-term prevention of relapse. One of the factors affecting the result of both acute and long-term therapy is patient adherence to administration of antipsychotics. Adherence/nonadherence to treatment may be viewed as nonadherence to appointments with a psychiatrist, irregular outpatient visits, discontinuation of outpatient treatment, refusal to come to psychotherapeutic and/or psychoeducative sessions, and other psychosocial activities (Compton, 2006). These factors, such as nonadherence to medication and nonadherence to medical appointments and outpatient treatment are interrelated, affect each other, and have common causes.

4.3.2. Adherence to treatment: definition and description

Adherence to treatment is a general indicator of the quality and success of communication between the physician and the patient. Adherence refers to the will of the patient to observe the physician's recommendations. In contrast to the previously used term "compliance", adherence emphasizes the active role of the patient, as opposed to passive subjection to a physician's authoritative directions (Fawcett, 1995). Adherence to treatment refers to the extent to which patient behaviour, in terms of taking medications, following diets, or executing lifestyle changes, coincides with the medical or health advice (Awad et al., 2004). Adherence to medication involves a whole range of types of patient behaviour from treatment and medication refusal (nonadherence) to irregular use or a partial change of daily medication doses (partial adherence). Partial adherence to psychotropic drugs including antipsychotics is at least just as frequent as total nonadherence.

Clinical research focused on psychiatric patients has shown that about one-third of patients are fully adherent, one-third are partially adherent, and the last one-third are nonadherent (Wricht, 1993; Oehl et al., 2000; Marder et al., 2003). Psychotics are nonadherent not only to antipsychotic drugs, but also to other drugs such as antidiabetics, antihypertensives, hypolipidemics, and others (Dolder et al., 2003).

4.3.3. Prevalence of nonadherence to antipsychotic therapy

Nonadherence to antipsychotic therapy in patients with schizophrenia is far more widespread than clinicians assume. Byerli et al. (2002) monitored nonadherence to therapy using an electronic Medication Event Monitoring System (MEMS method) in 21 patients with schizophrenia for 3 months. Attending physicians assumed nonadherence in 5% of patients, but electronic monitoring of medication intake showed that as many as 62% of patients were fully or partially nonadherent in reality. Patients' reports of nonadherence to pharmacological therapy were found by Lam et al. (2002) to be 2.7 times less frequent than nonadherence observed during routine antipsychotic plasma levels testing. Compared to patients with chronic somatic diseases (such as hypertension, epilepsy, arthritis, or diabetes), nonadherence to treatment in schizophrenia is similar..

In cross-sectional studies, 40%–55% of outpatients with schizophrenic disorder were nonadherent to oral administration of conventional antipsychotics (Fenton et al., 1997; Lacro et al., 2002). Cramer et al. (1998), who analyzed 24 studies, found the rate of nonadherent outpatients to be 42% (13%–76%); in another 7 studies, nonadherence was detected by toxicological urine testing and confirmed in 40% (22%–65%) of patients. An analysis of 21 studies including 2861 patients with schizophrenic disorders, published from 1983–2002, found nonadherence to antipsychotic therapy in 44% of patients (see Table 1).

Nonadherence can develop in the initial stages of schizophrenia. In two studies of patients with a history of one schizophrenic episode, nonadherence was detected in 37% to 41% of patients (Mojtabai et al., 2002; Coldham et al., 2002). A total of 25% of patients were nonadherent as early as 7–10 days after the hospital release (Lam et al., 2002). Among 200 patients after their first episode of schizophrenia, 39% were nonadherent and 20% partially adherent to antipsychotic therapy during the first year of monitoring (Coldham et al., 2002). The nonadherence rate among patients rose as high as 75% after 2 years (Weiden et al., 1997; Lam et al., 2002). Another study including 1619 patients with schizophrenia treated with antipsychotics for 2 years involved similar monitoring; 24% of patients were fully and 16% partially nonadherent (Gilmer et al., 2004).

Higher adherence to second-generation antipsychotics compared with conventional antipsychotic medications has already been indicated by early

reports (Voruganti et al., 2002; Rabinowitz et al., 2001; Hellewell et al., 1999; Bartko et al., 2002). Dolder et al. (2002) found that 43% of 288 outpatients with schizophrenia in a 3-month therapy course were nonadherent, compared with the 50% nonadherence rate identified in conventional antipsychotic therapy ($p < 0.05$). Converted to refer to a 12-month period, the figures indicate that patients did not take conventional antipsychotics 7 days in a month and took second-generation antipsychotics only 4 days in a month on average (Voruganti et al., 2002).

A clozapine prescription reduced the risk of nonadherence by more than half, and patients remained adherent to therapy longer than in administration of conventional and also other antipsychotics of the second generation (Weiss et al., 2002; Cooper, 2003). The fact that clozapine is associated with better adherence than other antipsychotic drugs has been confirmed by Claghorn et al. (1987) and Rosenheck et al. (2000). The Pan-European SOHO (Schizophrenia Outpatient Health Outcomes) study found nonadherence to be the lowest for clozapine and olanzapine (Novick, 2005). Olanzapine adherence was higher than risperidone adherence (Cabeza et al., 2000). Patients after their first episode of schizophrenia were at a 1.5 times higher risk of nonadherence than patients treated with olanzapine (Perkins et al., 2006).

An adherence improvement of 28% was recorded in association with a switch from conventional to atypical antipsychotics (Voruganti et al., 2002). In contrast, Diaz et al. (2004), Nakonezny et al. (2006), Valenstein et al. (2004), and Menzin et al. (2003) found no difference in treatment adherence between classic and atypical antipsychotics. Therefore, further long-term studies are needed to make possible an ultimate assessment of differences in adherence to first- and second-generation antipsychotic therapy.

In an open study including 85 nonadherent outpatients with schizophrenia and schizoaffective disorders, olanzapine in the form of fast-soluble tablets was administered for 6 weeks (Kinon et al., 2003). In addition to a significant improvement in the psychic status measured on PANSS, a significant reduction of nonadherence on the Rating of Medical Influences (ROMI) (Weiden et al., 1994) scale was observed. Four out of seven factors derived from ROMI were significantly improved as early as from week 1 on: medication benefit, denial of illness, outside opposition, and medication side-effect. In another open 6-month study, risperidone solution was administered, and most of the 81 patients preferred this galenic form (Jasovic-Gasic et al., 2005).

4.3.4. Consequences of nonadherence to antipsychotic treatment

The consequences of nonadherence include exacerbation of symptoms, increased relapse rate, psychiatric hospitalisation, and less favourable patient prognosis (Weiden et al., 1995; Dolder et al., 2003; Keith et al., 2003). A relapse means an additional burden for the family/partner, an increased crisis-intervention rate, an increased risk of alcohol and drug abuse, and increased health care consumption (Coldham et al., 2002). Other consequences of a relapse may include loss of work position or loss of the job, loss of accommodation, loss of support from the environment, and loss of patient morale and therapeutic motivation. Relapse resulting from nonadherence is often wrongly attributed to antipsychotic treatment inefficacy. Recurring relapses lead to diminished tolerance of stress situations by the patient, symptom persistence, greater difficulty in achieving disorder stabilization and maintaining its quality, and sometimes even to treatment resistance.

According to Novak-Grubic et al. (2002), relapses occur in 70% of patients nonadherent to antipsychotic therapy as opposed to the 19% rate observed in adherent patients. A total of 54% to 82% nonadherent patients experienced a relapse within one year after their first schizophrenic episode (Novak-Grubic et al., 2002; Robinson et al., 1999). Withdrawal from antipsychotic treatment after a first schizophrenic episode increases the risk of relapse up to 5 times. As far as the further development of schizophrenic disorders is concerned, up to 3.5% of patients experience a relapse every month of depot antipsychotic therapy in contrast to the 11% patients free of therapy (Weiden et al., 1995).

A relapse of schizophrenia occurs in a majority of patients who have withdrawn from antipsychotic treatment, but also in those who have continued the therapy. Many patients may feel well initially after withdrawal from antipsychotic treatment and sometimes even feel better when undesirable effects disappear. Exacerbation of symptoms of schizophrenia may occur within several months and a relapse will set in, but involuntary hospitalisation and a longer and more serious relapse are more often the case (McEnvoy et al., 1984). The relapse after premature withdrawal from antipsychotic treatment is often associated with suicidal behaviour or violence (Jokerson et al., 1983). Nonadherence to antipsychotic medication is also a risk factor for the development of violent behavior in schizophrenic patients (Mohr et al., 2005). Relapses occurring despite continuous antipsychotic treatment are, conversely, fast to develop and mostly associated with affective symptoms (anxiety, depression);

they often occur after external stress, hospital admission is mostly voluntary, and the relapse fades away quickly.

A relapse of schizophrenia may lead to hospitalisation: 50%–75% of all rehospitalisations in patients with schizophrenia are a consequence of nonadherence (Ayuso-Gutierrez et al., 1997; Ascher et al., 2003). In a study by Gilmer et al. (2004) including 1619 patients with schizophrenic disorders, 41% of patients were adherent to treatment, 24% were nonadherent, and 16% partly adherent. Yearly rehospitalisation rates were 14%, 35%, and 24% among adherent, nonadherent, and partly adherent patients, respectively. The number of admissions to hospital wards other than psychiatric was also lower among patients adherent to antipsychotic therapy – see Table 2.

A correlation between adherence to antipsychotics and risk of hospitalisation was confirmed by another two studies. The first involved 4325 patients with schizophrenia monitored for 1 year (Weiden et al., 2004). The negative impact of even partial adherence was demonstrated; the more days patients did not take medication, the higher the risk of rehospitalisation was. The other study also demonstrated that 23% of patients who were rather nonadeherent to antipsychotic treatment were rehospitalised compared with a mere 10% of those with good adherence (Valenstein et al., 2002). In addition, the number of days of rehospitalisation per year was higher among those who were partially adherent compared with adherent patients (33 days vs. 24 days on average). Nonadherence was associated with a 1.5 higher rate of use of hospital care and an almost three-fold increase in indirect costs (Knapp et al., 2004). Another potential consequence of nonadherence to treatment in patients with schizophrenia may be their suicidal behaviour. Out of 41,754 patients with schizophrenia, 1,020 attempted a suicide and 154 of them died (Ward et al., 2006). In this study, full adherence was recorded in 61% of patients, partial adherence in 16%, and nonadherence in 23%. Fully adherent patients had a significantly lower hospitalisation rate, suicide rate, and completed suicide rate over the 2.6 years of monitoring.

Another study also demonstrated the risk of suicidal behaviour as a consequence of nonadherence. Among the 603 patients with schizophrenic disorder, 33% were nonadherent (the criterion was a failure to take antipsychotic medication for 30 days or more) (Herings et al., 2003). Suicide attempts were four times more frequent among nonadherent patients compared with fully adherent ones.

4.3.5. Causes of nonadherence

The overview of all risk factors for nonadherence to antipsychotic medication and/or follow-up appointments are schematically presented on Table 3 (Compton, 2006).

The likely causes of nonadherence can be categorized into 4 groups:

1) Causes derived from the schizophrenic disorder itself

Important causes of nonadherence related to schizophrenia include poor insight, higher disorder intensity expressed by a higher PANSS score, prevailing negative symptomatology (e.g., apathy, hypobulia, alogia), cognitive deficit and forgetfulness, depression, loss of motivation to therapy, duration of illness, and current alcohol and drug abuse (Mutsatsa et al., 2003; Tattan et al., 2001; Hummer et al., 2000; Hudson et al., 2004). Neurocognitive deficit correlates with lower adherence to medication after 6 months (Cuffel et al., 1996). Nonadherence is also associated with anosognosia, independent of other demographic and clinical patient characteristics (Droulout et al., 2003). Some authors believe that anosognosia is a stronger predictor of nonadherence than therapeutic efficacy of antipsychotic medication and its adverse effects. Comorbid drug addiction in association with nonadherence leads to more frequent rehospitalisations. The average time to first rehospitalisation in 99 patients monitored for 4 years was 37 months; it was shorter by 10 months in patients with drug abuse and shorter by another 5 months when drug abuse was simultaneous with nonadherence (Hunt et al., 2002). In addition, the mean length of hospitalisation in adherent patients with comorbid drug abuse was longer than that observed in adherent patients who did not abuse drugs (mean times 32 days vs. 18 days).

2) Patient characteristics

Nonadherent patients are largely young and male, live on their own without any support from their environment, are from lower socioeconomic groups, and have poor contact with medical staff. Personal histories of patient nonadherence to psychotic therapy include nonadherence significantly more frequently. Families of these patients largely have a negative or ambiguous attitude to the patient's therapy (Awad et al., 2004; Olfson et al., 2000).

3) Causes associated with the health-care system

The causes behind nonadherence may, among other things, be low or too-complicated availability of psychiatric care, its financial costs, and low quality of cooperation between the physician and the patient. Adherence also depends on the frequency of medical visits or at least interviews with a nurse; adherence to clozapine treatment was found to be higher in patients undergoing regular blood count checks (Patel et al., 2005).

Adherence to antipsychotic treatment also depends on whether or not the patient turns up for a check-up after discharge from the hospital. According to Kruse et al. (2003a, 2003b), only 18%–36% of patients discharged from the hospital turned up for a check-up. There was a 4 times higher likelihood of a medical check-up in patients who had an outpatient appointment within 2 weeks of hospital release compared with those who were invited after more than 2 weeks. Failure to turn up for a follow-up examination can be predicted in patients discharged against doctors' advice, without the future attending psychiatrist being chosen, after over 2 weeks after release from the hospital, and in case of problems in support groups (family, marriage etc.) (Compton, 2006).

4) Causes associated with antipsychotic treatment

Pharmacological causes of noncompliance include treatment inefficacy, too-complicated dosage, polypharmacy as opposed to monotherapy, and the social stigma of medication taking (Kruse et al., 1990; Diaz et al., 2004). Important causes of nonadherence are undesirable effects of antipsychotics, the most frequent of which are extrapyramidal symptoms, especially akathisia, antipsychotic-induced dysphoria, obesity, and sexual dysfunction (Van Putten et al., 1974, 1984; Crookson et al., 1991; Fleischhacker et al., 1994; Weiden et al., 2004; Pfeifer et al., 1991). Undesirable side-effects of antipsychotics account for 25% to 66% of all reasons for treatment discontinuation among patients (Fenton et al., 1997).

4.3.6. Predictors of nonadherence

From the 1970s to the 1990s, the undesirable side-effects of antipsychotic drugs were held to be the most important predictors of future nonadherence (e.g. van Puten, 1974; Buchanan, 1992; Fenton et al., 1997). Later on,

attention turned to other risk factors. The predictor of future adherence currently believed to be the most reliable one is previous adherence to treatment (Ascher-Svanum et al., 2006). Patients adherent to treatment over a recent 6 months were 4.14 times more likely to be adherent to antipsychotics in the next year. Previous full adherence to therapy predicted future adherence in 78.5% of patients with schizophrenic disorders. On the other hand, previous nonadherence predicted future nonadherence in a mere 44% of patients. It can be concluded from these findings that nonadherence can be influenced and is transitory. These authors tested the correlation of 21 risk factors with adherence to therapy; 5 out of 21 factors were the most successful predictors: previous adherence, drug abuse, alcohol abuse, previous antidepressant therapy, and relatively high subjective cognitive deficit. Repeated and more sensitive analysis confirmed these factors and added the factor of depression/anxiety (measured on PANSS) at the time of the evaluation. Dependence of nonadherence on cognitive deficit was identified in a study by Donohoe et al. (2001), and persisting drug abuse as a risk factor was found by Lambert et al. (2005).

The finding that nosognosis is an important factor was confirmed by studies by Rittmannsberger et al. (2004) and Kamali et al. (2006). The former of these studies found that adherence to medication was better in people who were in regular contact with their psychiatrist. A previous study involving 162 psychotic patients in outpatient therapy had already established that the level of adherence depended on the working alliance with the therapist and/or attending staff during hospitalisation (Weiss et al., 2002; Olfson et al., 2000).

Another risk factor for nonadherence is refusal of the patient's family to get involved in the therapy upon his/her hospitalisation (Olfson et al., 2000). Attention has also concentrated on the possibility of predicting nonadherence as early as during the first episode of schizophrenia. These studies identified predictors of nonadherence similar to those observed in chronic patients with recurring episodes, especially anosognosia, cognitive dysfunction, persisting drug abuse, and a high intensity of positive symptoms of schizophrenia (Novak-Grubic et al., 2002; Kamali et al., 2006). Perkins et al. (2006) emphasize the importance of a patient's conviction of the necessity and benefits of treatment as early as after the first schizophrenic episode. In 2005, Compton et al. identified eight major independent predictors of nonadherence in a group of 1843 patients with a schizophrenic disorder: (1) substance abuse, (2) moderate-to-severe psychotic symptoms, (3) medication side-effects, (4) personality disorder, (5) economic problems, (6) prior hospitalisation, (7) low

Table 4.3.1. Frequency of non-adherence to antipsychotic drugs among schizophrenic patients

Author(s), year	No. of patients	Treatment duration (months)	Nonadherence (%)
Dolder et al., 2002	225	12	50 (CAP)
			43 (SGAP)
Mojtabai et al., 2002	182	12	37
Coldham et al., 2002	200	12	41
Svarstadt et al., 2001	424	12	31
Olfson et al., 2000	213	3	19,2
Rastagi et al., 2000	31	6	32
Luchins, 1998	28	12	25 (clozapine)
Agarwal et al., 1998	73	23	62
Duncan et al., 1998	90	12	45
Ruscher et al., 1997	148	NA	47
Nageotte et al., 1997	202	10	47
Owen et al., 1996	135	6	15
Budd et al., 1996	40	12	50
Razali et al., 1995	225	NA	73
Buchanan et al., 1992	61	12	41
Frank et al., 1990	143	24	61
McEvoy et al., 1989	46	30	53
Drake et al., 1989	115	6	26
Bartko et al., 1988	58	12	54 (depot AP)
Gaebel et al., 1985	72	12	40
Hogan et al., 1983	150	12	54
Total: 21 studies	**2861**	**3–30**	**19.2%–73%; median 44%**

CAP: conventional antipsychotics; SGAP: second-generation antipsychotics; depot AP: long-acting conventional antipsychotics

GAF (Global Assessment of Functioning), and (8) short duration of treatment with the current psychiatrist.

The following factors contribute to the nonadherence to antipsychotics (Compton, 2006): impaired insight, substance abuse, a higher level of positive symptoms, conceptual disorganization, hostility, suspiciousness, cognitive deficit, negative attitudes toward medication, week therapeutic alliance, prior history of nonadherence, low family and social support, problems with transportation, problems with living arrangements/housing instability, the cost of

medication, lack of insurance, poor physician–patient relationship, and medication side-effects, especially akathisia.

The same author addressed not only nonadherence to antipsychotics, but also nonadherence to follow-up. Between 30% and 60% of patients do not attend their first outpatient appointment after hospitalisation. Patients who do not turn up for the first outpatient follow-up are at a 2 times higher risk of rehospitalisation within the next 12 months (Nelson et al., 2000). Compton regards as the key predictors of nonadherence to follow-up outpatient treatment, involuntary hospitalisation, failure to appoint the future outpatient psychiatrist, low social support, and a too-long interval between hospital release and the planned follow-up. Another study listed as the key predictors of nonadherence to outpatient psychiatric treatment young age, low family support, no prescribed psychotropic drugs, lack of health insurance, and Hispanic origin (Kruse et al., 2002).

A list of all risk factors of nonadherence to outpatient psychiatric treatment and antipsychotic medication is presented in Table 4.3.1. (Compton, 2006).

4.3.7. Adherence/nonadherence measurement

Adherence/nonadherence are measured using direct or indirect methods (Sleator, 1985). Direct methods include determination of serum drug concentrations and of the drug (or its metabolite) in the urine. Another option is using a so-called drug marker, which is administered along with the drug under investigation. The drug marker may be detected, for example, in the urine by colour (e.g., riboflavin). Reliability of adherence measurement based on riboflavin has been confirmed by several studies (Jones, 1967; Camfield et al., 1979). Jay et al. (1984) used 28 mg of riboflavin in children, and the likelihood of detecting adherence or nonadherence was 90%. The authors pointed out that 1/26 persons was a fast metabolizer and the negative finding in the urine was false.

The recommendation is to detect the antipsychotics under analysis at irregular intervals. Determining drug concentrations in blood is demanding, expensive, and sometimes even impossible (e.g., because the effective concentrations are not known for all drugs).

Indirect methods of finding about adherence/nonadherence to medication include counting tablets by medical staff, returning prescription bottles by the patient, monitoring prescription collection by pharmacists, or electronic monitoring. MEMS records electronically every occasion on which a box containing medication is opened, but not whether the patient has really taken the medication. The recommendation is to prefer indirect questions to find out about potential discrepancies between the number of tablets prescribed and taken to returning bottles with remaining medication and tablet counting: Effective questions are those addressing whether the patient needs more medication compared with the last check-up or whether the medication is sufficient and no other prescription is needed.

When adherence is being tested, the physician needs to evaluate not only the patient's statements, but also behaviour, attitudes, and psychopathology. Information from multiple sources is useful because patient statements often do not correspond to reality and tend to be exaggerated.

One extensively used indirect method of adherence/nonadherence identification in clinical practice is the use of various subjective questionnaires and scales or diaries with records of drug taking. Some authors believe the reliability of questionnaires to be higher than that of clinical interviews. The most frequently used questionnaires include the Drug Attitude Inventory (DAI-30 and its abridged version DAI-10) (Awad, Hogan et al., 1983, 1992), ROMI, and MARS (Medication Adherence Rating Scale – Thompson et al., 2000). A whole range of other subjective questionnaires has been developed, but their use has not, however, become widespread in clinical practice; these include the Neuroleptic Dysphoria Scale (NDS) (Van Putten et al., 1978), the Subjective Wellbeing on Neuroleptic Scale (SWN) (Naber et al., 1994), the Insight and Treatment Attitudes Questionnaire (ITAQ) (McEnvoy et al., 1989), Attitudes Toward Neuroleptic Treatment (ANT) (Kampman et al., 2000), Medication Management Ability Assessment (MMAA) (Patterson et al., 2002), Personal Evaluation of Transition in Treatment (PETiT) (Lakshmi et al., 2002), and the Brief Evaluation of Medical Influences and Beliefs (BEMID) (Dolder et al., 2004). The description and characteristics of some of these questionnaires can be found in the review by Awad et al. (1996).

4.3.8. Nonadherence to treatment

Considering the serious consequences of nonadherence, strategies that would lead to improving the attitude of patients towards treatment and medical recommendations are very important – see Table 4. There is ongoing evidence that various psychosocial and psychotherapeutic interventions may improve adherence to drug treatment, including patients denying their psychotic disorder or homeless mentally ill (Kane et al., 1997; Kemp et al., 1999; Dixon et al., 1997). Interventions focus on issues concerning medication therapy and medical care organization.

4.3.8.1. Medication therapy

When selecting an antipsychotic, the psychiatrist should consider the expected benefits of the treatment against its adverse effects and financial demands. The decision-making process should involve the patient and/or his/her family, too (shared decision-making, Haman et al., 2005). Better efficacy and tolerability characterize antipsychotics of the second generation; their administration can, however, be associated with undesirable metabolic effects such as weight gain or dyslipidemia.

Administration of antipsychotics once a day in outpatient treatment led to a significantly better adherence within 3 months compared to administration of 2 or 3 doses per day (Diaz et al., 2004). The study compared adherence to olanzapine, risperidone, and first-generation antipsychotics. The best results were achieved with olanzapine.

Apart from the once-daily administration, the psychiatrist should also choose an optimal galenic form because antipsychotics of the second generation are now available as fast-soluble tablets or drops. The optimal solution for patients whose treatment nonadherence to oral antipsychotics was repeatedly identified are intramuscular depot injections. The physician should carefully titrate the daily dose of the antipsychotic to achieve maximum therapeutic efficacy with a minimum of adverse effects. The financial contribution towards the cost of the antipsychotic should not discriminate patients with a schizophrenic disorder.

The psychiatrist and the medical staff should analyze the availability of medical care to the patient and his/her potential transportation problems. If the

patient is hospitalised, s/he should know the name, address, phone number, and hours of attendance of the attending psychiatrist prior to release. It is good if the patient can establish contact with the future attending psychiatrist before discharge from the hospital. If the patient is to return to the same institution for outpatient follow-up, s/he should be acquainted with the layout plan of the clinic or hospital. The importance of planning a timely check-up after hospital discharge was demonstrated in the study undertaken by Nelson et al. (2000). There were 542 persons (17%) among the 3113 patients who were rehospitalised; 406 never attended a single psychiatric check-up after the hospital release and 15%–29% of these patients were rehospitalised while only 10% of patients had to be rehospitalized in the group of patients who came for regular follow-up examinations. Patients who did not turn up for any psychiatric check-up after hospital release had a 2 times higher likelihood of rehospitalisation within 12 months. Patients who turned up for an outpatient follow-up examination within 14 days of the dismissal were more adherent both to outpatient visits and treatment. Adherence was significantly enhanced by reminders on the part of the physician, invitations by mail, or telephone reminders (Macharia et al., 1992). In case of cognitive deficit, medication boxes, alarm bells, telephone reminders, or the assistance of a close person checking that the medication is taken are recommended.

Making sure that the treatment is supported by the patient's family, spouse, and/or other caretakers is another very important factor. These support groups can also serve as a potential source of information on the patient's behaviour, regularity of drug-taking, attitudes to treatment, and/or potential checks of medication-taking and coming for outpatient visits on the part of the patient.

The psychiatrist should always carefully listen to the subjective difficulties of the patient, forming a therapeutic alliance or concluding a therapeutic agreement with the patient. The psychiatrist and other medical staff should provide the patient with very specific advice and recommendations in response to very specific situations. The more frequent the patient's contact with medical staff, the better the adherence (Patel et al., 2005).

Efficacy of interventions aimed at improving adherence in patients with schizophrenia was evaluated by Nosé et al. (2003), Dolder et al. (2003), and Zygmunt et al. (2002). In those studies, the efficacy of various kinds of intervention was demonstrated in 33%–62% of patients with a schizophrenic or schizoaffective disorder.

Nosé et al. (2203) conducted a metaanalysis of 24 randomized studies with a total of 3272 patients. The median duration of interventions was 24 weeks. Depending on the type of intervention, efficacy of psychoeducation was analyzed in 14 studies, of psychotherapy in 3 studies, of telephone assistance in 2 studies, and of specific procedures in 5 studies. All interventions reduced nonadherence more than twice compared with conventional care. The most efficient interventions were family therapy, better planning and better availability of psychiatric care and psychotherapy; the least efficient were psychoeducation and telephone assistance.

Dolder et al. (2003) analyzed results of interventions aimed at improving adherence to antipsychotics in a total of 21 randomized studies. Twenty-three types of intervention were tested. Eleven of twenty-one studies concerned outpatient treatment. It may be said that overall efficacy of the interventions was confirmed in 13/21 studies, namely in 15/21 types of intervention. Six of twenty-one studies included only patients nonadherent to therapy; three of these demonstrated significant efficacy of the interventions. The authors found that psychoeducation was the least efficacious to non-efficient (in one-quarter of the studies) and on the other hand, that combined strategies were the most efficacious (efficiency in 6/11 studies).

Zygmunt et al. (2002) analyzed results of interventions aimed at adherence improvement in a total of 39 studies; in only 33% of studies, therapeutic intervention had a sufficient effect. Psychoeducation of the patient and his/her family were again insufficiently efficient. Cognitive–behavioural therapy and motivation techniques were more efficient than behavioural techniques. Combined interventions were the most efficient (in 55% of studies), involving motivation and problem-solving techniques and/or a behavioural component and focused on nonadherence and social support. Interventions focused specifically on nonadherence were more successful than generally oriented techniques. The number of sessions was not decisive for intervention efficacy.

What was surprising about all three analyses was the low efficacy of psychoeducation in terms of nonadherence reduction. The efficacy of psychoeducation was not higher even when it was based on a peer-to-peer or a family-to-family system. One of the few positive studies was that by Pitschel-Walz et al. (2006), in which psychoeducation was a more efficient tool of influencing adherence than conventional care. Most authors concluded that psychoeducation improved the knowledge of the patient and his/her family about schizophrenia and its treatment, but did not change their attitudes. On the other

hand, in a metaanalysis of 25 studies, psychoeducation reduced the number of relapses by 20% (Pitschel-Walz et al., 2001) and in another analysis of 10 studies, it was also found to be an efficient tool in relapse prevention (Pekkala et al., 2002). This discrepancy between the studies has not been explained.

The existing experience has been used as a basis for developing the so-called "compliance therapy" involving cognitive–behavioural and motivation techniques and stressing the merits and risks of antipsychotic therapy (Kemp et al., 1996). Compliance therapy proved more effective than conventional counselling in a randomized controlled study (Kemp et al., 1996). The improvement lasted even after 6 and 18 months (Kemp et al., 1999). Patients in the compliance therapy group were also less often rehospitalised within 18 months, and their attitude towards the illness and their social functioning also improved. These findings were unfortunately not confirmed by another two studies. O'Donell et al. (2003) did not find compliance therapy more successful than conventional counselling and did not identify any effect on the number or length of rehospitalisations over 1 year. Byerly et al. (2005) did not find compliance therapy to have any effect on adherence to antipsychotics in 30 outpatients monitored for 5 months. The study used MEMS to measure adherence. All of the three above-described studies worked with a similar scheme of 4–6 sessions lasting for 30–60 minutes.

4.3.9. Summary

Both full and partial nonadherence are high-risk factors in antipsychotic treatment; they may reduce therapeutic efficacy of medication or increase the incidence of relapses, rehospitalisations, or suicidal and aggressive behaviour of patients with schizophrenia. Nonadherence enhances the use of medical services and associated financial costs. Psychiatrists tend to underestimate nonadherence to treatment and medication while adherence can be observed in only 30%–50% of patients. The main causes of nonadherence are schizophrenia itself and the ensuing anosognosia, paranoia, and cognitive deficit; it is also exacerbated by low support on the part of the patient's social environment, a poor attitude to medical staff with little contact, poor availability of outpatient care, and overcomplicated and unsuitable medication administration regimens. The most reliable predictors of nonadherence are a personal history of nonadherence, current drug abuse, cognitive deficit, and high intensity of psychotic symptoms, low social support, economic aspects of treatment, and inefficiency or serious adverse effects of antipsychotic ther-

apy. The means of influencing nonadherence are the choice and administration scheme of antipsychotics, improving the availability of outpatient treatment and its planning, ensuring social support for the patient, and improving contact with the patient. The interventions that proved successful in reducing nonadherence combined cognitive–behavioural, motivation, and education techniques aimed at attitudes towards treatment and medication on the part of the patient and the persons close to him/her.

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