

Improving Adherence to Antipsychotic Pharmacotherapy

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Abstract: Objective: To review the consequences of nonadherence to antipsychotic pharmacotherapy in patients with schizophrenia, as well as associated risk factors for nonadherence and methods of improving adherence.

Methods: Review of the literature based on a MEDLINE search on the terms schizophrenia and adherence or compliance, limited to the English language, supplemented by the author's own knowledge of the topic.

Results: Nonadherence to antipsychotic therapy is a common reason for relapse and rehospitalization of patients with schizophrenia and thus contributes to the high cost of treating psychoses, adverse events, and lack of insight. Comorbid substance abuse, little family involvement, and a poor clinician-patient relationship are among the risk factors for nonadherence. Patients with a negative attitude towards treatment, which can result from adverse events, are also more likely to be nonadherent. Strategies to improve adherence include optimizing antipsychotic therapy, minimizing adverse events, encouraging patient participation in psychoeducational programs, treating comorbid substance abuse disorders, involving family members in the treatment process, and forging a close therapeutic relationship with the patient.

Conclusions: Improving adherence is difficult but necessary for achieving optimal treatment outcomes. Careful selection of drug therapy, with emphasis on a drug's tolerability, combined with nonpharmacologic interventions, may help decrease nonadherence in patients with schizophrenia.

Keywords: Adherence, Antipsychotic, Nonadherence, Schizophrenia.

INTRODUCTION

Adherence, sometimes referred to as compliance, reflects the frequency with which a patient takes medication as prescribed. There is a large body of evidence on this topic, and this article attempts to review the key areas of discussion in the literature. It is based on a general MEDLINE search, supplemented by the author's knowledge of the topic.

Nonadherence with medication is often an issue in medical disorders that tend to be asymptomatic, such as hypertension and diabetes mellitus. Among patients taking antihypertensive medication, adherence rates at 1 year range from 5% for patients taking thiazide diuretics to 75% for those treated with angiotensin-converting enzyme inhibitors [1]. Among patients with diabetes, those taking multiple medications that require frequent dosing tend to be less adherent than those given more simplified medication regimens [2].

For patients with schizophrenia, the disorder is not asymptomatic, and the symptoms themselves may impede adherence. Taking medication as prescribed is particularly important for those with schizophrenia because the costs of nonadherence are considerable. With the prevalence of schizophrenia at about 1% of the adult population, treating this mental illness accounts for about 2.5% of total annual healthcare expenditures in the United States [3]. Although direct medical costs for schizophrenia are high (\$18.6 billion in 1991), indirect costs related to disability and lack of employment are even higher (\$46.5 billion in 1991) [4].

Contributing to these high costs are the early onset and chronic nature of schizophrenia, its long-term disabling effects, and a need for recurrent hospitalization and ongoing outpatient care [5].

With appropriate inpatient treatment, psychotic symptoms can be controlled in most patients with first-episode schizophrenia, but maintaining control of symptoms after discharge is more difficult. Some success has been reported with involuntary outpatient commitment, in which patients discharged to the community are under court order to adhere to treatment [6]. However, if maintenance pharmacotherapy fails and psychotic symptoms reappear, the patient is likely to require hospitalization, which is the most costly treatment setting for mentally ill patients [7].

For patients with schizophrenia, the risk of relapse (re-emergence of previously controlled symptoms) is high, with about 3.5% of patients per month relapsing after discharge [8]. Although many factors influence the risk of relapse, [9] the most common reasons are loss of antipsychotic efficacy and nonadherence to the antipsychotic regimen [10]. Among patients with psychiatric disorders, only about one third take medication as prescribed; one third take medication erratically, either taking a lower dose or missing doses; and one third do not take their medication at all [11]. Improving adherence to medication among the two thirds of patients who are nonadherent or partially adherent is one means of preventing, or at least postponing, relapse.

NONADHERENCE, RELAPSE, AND REHOSPITALIZATION

The risk of relapse is more than double in patients given placebo compared with those treated with antipsychotics, [12] provided the medication is taken as prescribed.

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Determining how well a patient is adhering to antipsychotic drug therapy can be difficult. Methods used to judge adherence include self-reporting by patients; tabulating pill counts and prescription refills; using electronic adherence monitors on pill bottle caps; and measuring drug concentrations in blood, urine, or saliva [10-13]; none of these methods, however, provides a completely reliable indication of adherence. Control of symptoms and other measures of clinical status cannot be used to assess adherence because relapse could also reflect loss of drug efficacy. Clinicians thus have limited means of accurately gauging the level of adherence among individual patients.

Nonetheless, efforts must be made to encourage adherence. Even partial nonadherence can lead to worsening symptoms and an increased risk of relapse and rehospitalization. In one study, irregular adherence was associated with an approximately 2-fold increase in hospitalizations and a 4-fold increase in total hospital days [14]. Even if nonadherent patients do not need to be hospitalized, poor adherence can compromise overall symptom control and social adjustment.

The mean rate of nonadherence with antipsychotic medication in patients with schizophrenia in the community is about 40% to 60% [15]. Among patients discharged on conventional antipsychotics, such as haloperidol, about 40% discontinue treatment within 1 year and 75% within 2 years [16,17]. Within the first 3 months after discharge, about 20% of patients miss 1 week or more of oral antipsychotic medication [18]. With each missed day of medication, the risk of rehospitalization increases. The risk is 4 times higher among patients who miss 30 days or more over 1 year compared with those who take medication as prescribed [19].

Each month after discharge, about 8% of patients stop taking antipsychotics, causing a 3-fold higher monthly incidence of relapse (11% with nonadherence versus 3.5% with good adherence) [7]. At a relapse rate of 3.5% of patients per month with good adherence, about 40% of patients would relapse within 1 year; at a relapse rate of 11% of patients per month with poor or no adherence, nearly all patients would relapse within 1 year [20].

Clearly, medication nonadherence is a strong predictor of relapse and rehospitalization. Among 63 "revolving-door" patients (those with frequent rehospitalizations) for whom complete medical histories were available, the most common reason for rehospitalization was nonadherence, accounting for 50% of cases [21]. Similarly, in another study of revolving-door patients, nonadherence to maintenance therapy and comorbid substance abuse showed the strongest correlation with rehospitalization [22].

RISK FACTORS FOR NONADHERENCE

Identifying patients at greatest risk for nonadherence may help clinicians focus efforts on those least likely to take medication as prescribed. In addition, some risk factors, such as medication tolerability, can be modified, thereby increasing the likelihood of adherence. As summarized in Table 1, risk factors for nonadherence or poor adherence can be categorized as related to the patient, disease, physician, or antipsychotic medication [13,15,18, 23-28].

Table 1. Risk Factors for Nonadherence in Patients with Schizophrenia

<p>Patient or Disease Related</p> <ul style="list-style-type: none"> Comorbid substance abuse Family members uninvolved in treatment or employed History of nonadherence Severe psychopathology Negative attitude toward treatment Poor insight into illness Shorter duration of illness or episodic course of illness Young or earlier age of onset of schizophrenia Forgetfulness Stigma of taking medications
<p>Physician Related</p> <ul style="list-style-type: none"> Inadequate attention to medication adverse events Inadequate discharge, planning, or lack of follow-up care Poor clinician-patient relationship Poor therapeutic alliance during hospitalization
<p>Treatment Related</p> <ul style="list-style-type: none"> Dose frequency, complexity, and route of administration Higher or lower antipsychotic doses Poor efficacy or slow onset of efficacy Possible use of conventional antipsychotics Tolerability and adverse events, particularly extrapyramidal symptoms and weight gain

From Agarwal *et al.*, [23], Casey, [26], Diaz *et al.*, [13], Fenton *et al.*, [24], Gerlach, [25], Lacro *et al.*, [15] and Olsson *et al.* [18] and Hudson *et al.* [70].

Patient-related risk factors encompass nonmodifiable risk factors, such as age and duration of illness, and those that could potentially be modified, such as comorbid substance abuse and lack of family involvement. For patients with a history of substance abuse, the risk of nonadherence is nearly 5 times higher than in patients without a substance abuse disorder [18]; with a history of nonadherence, the risk is 4 times higher, and for those whose family members do not become involved in treatment, the risk is 3 times higher [18].

Substance abuse disorders are one of the strongest predictors of patient nonadherence, suggesting that effective treatment of dual-diagnosis patients, although difficult, is necessary for increasing adherence to antipsychotic drugs [18].

Conventional antipsychotics seem to have little effect in controlling substance abuse, but atypical antipsychotics may be of benefit in managing these disorders [27]. Evidence of efficacy in decreasing abuse of alcohol, marijuana, or cocaine in patients with schizophrenia is greatest for clozapine, but quetiapine, risperidone, and olanzapine also appear to be effective for comorbid substance abuse disorders [18].

Physician-related risk factors for nonadherence are related primarily to poor relationships with patients, poor discharge planning, or lack of follow-up care. Not surprisingly, forming a good therapeutic alliance during hospitalization [18] and maintaining contact with outpatients [15] predict increased adherence. Involuntary outpatient commitment, in which clinicians can use law enforcement to ensure that

patients are examined and counseled about treatment, can also improve adherence [6].

Treatment-related risk factors for nonadherence include poor tolerability, dose frequency, higher antipsychotic dose, and possibly use of conventional antipsychotics. Both Lacro *et al.* [15] and Olfson *et al.* [18], reported that patients who adhere to medication tend to receive somewhat lower antipsychotic doses within the therapeutic range than do those who become nonadherent. Thus, improved adherence may allow treatment with lower doses.

Few data are available linking use of conventional antipsychotics with decreased adherence, or conversely, use of atypical antipsychotics with increased adherence. In the study by Olfson *et al.* [18], 17% of 172 patients who adhered to treatment were taking an atypical antipsychotic, compared with 7% of 41 patients who did not adhere to treatment, although the difference did not reach statistical significance. In a study using prescription fill rates to gauge adherence, Dolder *et al.* [28] reported a higher adherence rate at 12 months for patients taking atypical antipsychotics, particularly quetiapine, compared with those given conventional agents. The difference was not statistically significant, perhaps because of the relatively small number of patients enrolled (haloperidol, n=57; perphenazine, n=60; risperidone, n=80; olanzapine, n=63; quetiapine, n=28). In their review, Lacro *et al.* [15] found no consistent association between type of antipsychotic (conventional or atypical) and medication adherence. In more recent work, Diaz *et al.* [13] also found no difference in adherence between patients taking atypical antipsychotics (n=33) and those given conventional agents (n=17); the authors cautioned, however, that their results apply only to short-term adherence.

Interestingly, neither Lacro *et al.* [15] nor Olfson *et al.* [18] reported adverse events as a risk factor for nonadherence, although other authors have found such a link [10,24]. Thirty years ago, Van Putten [29] documented that patients who experienced extrapyramidal symptoms (EPS) were much more reluctant to take antipsychotic medication than were those who had no such symptoms. As Hellewell [30] points out, adverse events can negatively affect a patient's satisfaction with or attitude towards treatment, which can decrease adherence. Results of a telephone survey indicate that most patients taking antipsychotic medication experience adverse events, and in about one third of patients, these effects are severe or very severe [31]. Among the most common adverse events in patients taking conventional antipsychotics, atypical antipsychotics, or both, are; depression, sedation, difficulty thinking or concentrating, insomnia, dry mouth, muscle or joint stiffness, sexual dysfunction, weight gain, drooling (clozapine) and orthostatic hypotension [31]. Among the more serious adverse events are; EPS and tardive dyskinesia. Although patient tolerability of specific adverse events can vary, Casey [26] notes that for many patients, EPS, weight gain, and sexual dysfunction are especially likely to decrease adherence.

IMPROVING ANTIPSYCHOTIC TOLERABILITY

Both conventional and atypical antipsychotics are effective for psychotic symptoms, but prescriptions for atypical antipsychotics have been growing, perhaps because

of better tolerability [10]. In a study of Medicaid claims data from approximately 5000 patients, Rothbard *et al.* [32] found that use of conventional agents decreased from 79% in 1991 to 64% in 1996; by 1996, 39% of patients in this study were receiving an atypical antipsychotic. By 1998, atypical antipsychotics accounted for 51% of 11 million Medicaid-covered antipsychotic prescriptions, up from 17.5% of 9.1 million prescriptions in 1995 [33]. From 1995 to 1998, Medicaid prescriptions for atypical antipsychotics doubled, whereas those for conventional antipsychotics decreased by 25% [33]. Hellewell [30] reports that patient attitudes toward antipsychotic treatment are better with atypical antipsychotics than with conventional agents, which again may reflect improved tolerability.

Extrapyramidal Symptoms

Extrapyramidal symptoms, a disturbing adverse effect that can cause patients to discontinue treatment, are less likely to occur with atypical antipsychotics than with conventional drugs [11,26]. The incidence of other adverse events highly likely to decrease adherence, such as weight gain and sexual dysfunction, vary among antipsychotics.

The risk of EPS with conventional antipsychotics is well known. Overall, the risk of EPS with atypical antipsychotics is less than that for conventional drugs, but some differences among atypicals exist. In a review published in 2002, Tarsy *et al.* [34] examined data on the occurrence of EPS and tardive dyskinesia in patients taking atypical antipsychotics. They concluded that the risk of EPS and tardive dyskinesia is lowest with clozapine and quetiapine and somewhat higher with risperidone, ziprasidone and olanzapine; the risk appears to be dose dependent with the latter 3 drugs [35]. Data for aripiprazole is more limited; in general, the risk of EPS with aripiprazole appears to be low, although akathisia may be a problem at dosages of 15 mg/d or greater [36].

Weight Gain

Weight gain is distressing to patients [31] and, if great enough, can push patients into overweight or obese categories. Overweight is a body mass index of 25 to 29.9 kg/m²; obese is a body mass index of 30 kg/m² or more. Excess abdominal fat is typically present when waist circumference exceeds 40 inches in men and 35 inches in women. Excess weight not only negatively affects quality of life but also places patients at risk for serious medical conditions, including diabetes, hypertension, heart disease, stroke, and certain types of cancer [37]. Available evidence indicates that the greatest increases in weight occur in patients taking clozapine or olanzapine [38]; weight gain is less of a concern with quetiapine, risperidone, ziprasidone, and aripiprazole [36,40-43].

Sexual Adverse Effects

Although patients with schizophrenia may not be sexually active because of social withdrawal related to the mental illness, sexual dysfunction, including loss of libido and erectile and ejaculatory dysfunction, can result from use of antipsychotics that elevate prolactin levels [44]. Hyperprolactinemia also can lead to a range of medical problems, including amenorrhea, galactorrhea, gynecomastia

[44], and decreased bone mineral density [45], possibly leading to osteoporosis. Among the atypical antipsychotics, risperidone is most likely to cause hyperprolactinemia, with dose-related increases in prolactin seen in both men and women [44,46]. Clozapine appears to have little effect on prolactin levels, and no sustained elevations in prolactin have been found with ziprasidone or aripiprazole [47] or with quetiapine across its dose range [35,44,48]. (Comparison of side-effects associated with antipsychotic use is outlined in Table 2).

STRATEGIES FOR IMPROVING ADHERENCE

Improving adherence involves collaboration among the clinician, patient, and family members.

Optimal Antipsychotic Therapy

Selecting an effective antipsychotic that the patient can tolerate is the first step in improving adherence. Because EPS, weight gain, and sexual dysfunction appear to have the greatest negative impact on adherence [26], antipsychotics least likely to cause these adverse events should be the first choice for initial treatment.

The likelihood of improved adherence with atypical antipsychotics is reflected in lower long-term rates of rehospitalization in patients taking these drugs. In a case review study, Conley *et al.* [49] reported that 2 years after discharge, 34% of patients given risperidone and 13% of those given clozapine, had been readmitted, a rate of rehospitalization lower than that reported by other investigators for conventional antipsychotics. Rabinowitz *et al.* [50] found that rehospitalization rates for atypical antipsychotics and conventional agents were similar at 6 months and 12 months after discharge, but differentiated at

24 months (33% of patients given risperidone and 31% of those taking olanzapine had been readmitted by 24 months compared with 48% of those treated with conventional antipsychotics; $P=0.02$). Table 3 is a systematic review of studies to date comparing adherence rates with conventionals and atypical antipsychotics [122].

If initial drug therapy proves ineffective or intolerable, switching from a conventional antipsychotic to an atypical agent or switching from one atypical to another, may improve symptom control and tolerability and increase adherence [51]. In some cases, patients can be effectively maintained on conventional agents and need not be switched to an atypical drug. The most common reasons why patients remain on a conventional antipsychotic are, good response, patient choice, and physician choice [52].

Reduced-dose maintenance has been proposed as a means of minimizing adverse events and improving adherence [53]. However, the maintenance dosage must be adequate to control psychotic symptoms. Compared with standard-dose maintenance, low-dose and symptom-triggered maintenance regimens require more frequent use of rescue medication and may lead to relapse, limiting their usefulness [54].

Due to the fact that greater dosing frequency can deter adherence, antipsychotics that can be administered once daily may be preferred. Risperidone, olanzapine, and aripiprazole can be given once daily, according to the manufacturers' prescribing information [55-57]. Ziprasidone should be given twice daily with food [58]. Dosing for quetiapine is usually 2 times daily, but 3 times daily is also suggested [59]. Chengappa *et al.* [60], however, has reported that patients taking quetiapine can be switched from twice-daily to once a day dosing with no loss of efficacy.

Table 2. Comparison of Side-Effects Associated with Antipsychotic Use

Drugs	Extra-pyramidal Symptoms	Anti-cholinergic	Sedation	Orthostatic Hypotension	Weight Gain/Diabetes Mellitus ¹
Conventional					
Haloperidol	+++	0	+	++	+
Perphenazine	++	++	++	++	+
Thioridazine	++	+++	+++	+++	+++
Novel					
Clozapine	0	+++	+++	+++	+++
Olanzapine	+	+	++	++	+++
Quetiapine	+/0	0	++	++	+
Risperidone	+	0	+	++	+
Ziprasidone	+	0	+	++	+
Aripiprazole	+	0	+	+	+/-

0 = minimal to none; + = low; ++ = moderate; +++ = high¹ clozapine and olanzapine can cause diabetes mellitus independent of weight gain.

Table 3. Adherence with Conventionals Versus Atypical Antipsychotics

Authors	Database	Sample Size	Comments
Valenstein <i>et al.</i> 2004 [71]	Veteran Affairs Pharmacy	N=49,003 (one antipsychotic) N=14,211 (two antipsychotics)	<ul style="list-style-type: none"> Poor adherence with atypical (41.5%) vs conventional (37.8%)
Diaz <i>et al.</i> 2004 [13]	Randomized and non-randomized patients post discharge	N=33 (Olanzapine and Risperidone) N=17 (Conventionals)	<ul style="list-style-type: none"> Olanzapine was associated with an increased adherence compared to risperidone or conventionals.
Menzin <i>et al.</i> 2003 [72]	Medicaid Program	N=93 (conventionals) N=205 (atypicals)	<ul style="list-style-type: none"> Differences in adherence favored atypicals. Treatment with atypicals was associated with switching and reduced use of concomitant medication
Glick <i>et al.</i> 2002 [74]	Double-blind randomized clinical trial	N=1996 (olanzapine and haloperidol)	<ul style="list-style-type: none"> Olanzapine was superior to haloperidol using measures of study discontinuation, relapse and non-compliance
Dolder <i>et al.</i> 2002 [28]	Pharmacy refill records	N=57 (haloperidol) N=60 (perphenazine) N=80 (risperidone) N=63 (olanzapine) N=28 (quetiapine)	<ul style="list-style-type: none"> Medication adherence with clozapine was greater than with haloperidol due to greater symptom improvement and reduced side-effects.
Lacro <i>et al.</i> 2002 [15]	MEDLINE/HealthSTAR and PsycINFO databases	39 articles reviewed	<ul style="list-style-type: none"> Rates of non-adherence ranged from 41.2%-49.5%. No consistent association between type of antipsychotic (conventional or atypical) and medication adherence
Rosenheck <i>et al.</i> 2000 [73]	Double-blind randomized clinical trial	N=423 (clozapine and haloperidol)	<ul style="list-style-type: none"> Clozapine associated with greater continuation rates compared to haloperidol due to fewer side-effects and also improved symptoms
Rabinowitz <i>et al.</i> 2001 [50]	Israel's National Psychiatric Hospitalization Case Registry	N=268 (risperidone) N=313 (olanzapine) N=458 (conventional antipsychotics)	<ul style="list-style-type: none"> Rehospitalization rates on novel antipsychotics risperidone and olanzapine were not different from each other. However, atypicals had a considerably lower rate compared to conventional antipsychotics

When adherence is poor despite efforts to optimize oral pharmacotherapy, depot antipsychotics may be necessary. However, depot formulations of conventional antipsychotics are associated with the same adverse events as the oral drugs and may be less acceptable to some patients because of the need for regular injections [8]. A long-acting formulation of risperidone is available and requires intramuscular injection every 2 weeks.

Interventions to improve adherence includes optimizing pharmacotherapeutic treatments by incorporating psychosocial strategies. Psychoeducational programs with behavioral interventions based on motivational interviewing, problem solving, supportive services, family education, assertive community training are likely to improve adherence (Table 4).

Psychoeducational Programs

Psychoeducational programs can help patients understand schizophrenia, and may improve their attitude towards treatment [61, 62], both of which can improve adherence and therapeutic outcome [9]. Kelly *et al.*, [63] for example,

reported improved adherence among 418 outpatients with chronic mental illness who participated in 2 educational interventions (encouraging family members to actively participate in the treatment process and helping patients make better use of clinical services).

Participation in psychoeducational programs also has been associated with decreased rates of relapse and rehospitalization. An eighteen month, prospective, controlled study, showed that relapse and rehospitalization were significantly lower in patients who participated in a relapse prevention program (psychoeducation, active monitoring for early symptoms of impending relapse, aggressive intervention in patients with prodromal symptoms, weekly group therapy for patients, and group meetings for families) than in patients who received usual treatment (biweekly individual support sessions and medication monitoring) [64].

Atypical antipsychotics may be of particular benefit in conjunction with psychoeducational programs, because these agents, apart from their efficacy for positive and negative symptoms, may also improve cognition [11, 65].

Table 4. Intervention Studies Improving Adherence (Adapted from Zigmunt *et al.*)

Treatment Modalities	Studies	Comments
Individual Interventions	Kemp <i>et al.</i> , 1996, 1998 [75,76] Boczkowski <i>et al.</i> , 1998 [78] Macpherson <i>et al.</i> , 1996 [79] Streicker <i>et al.</i> , 1986 [85]	Motivational Interviewing and Cognitive approaches improved adherence. Behavioral Treatment> Psychoeducation Behavioral Treatment> Psychoeducation Psychoeducation = Standard care Psychoeducation = Standard care
Group Interventions	Malm <i>et al.</i> , 1982 [86] Atkinson <i>et al.</i> , 1996 [92] Battle <i>et al.</i> , 1982 [91] Seltzer <i>et al.</i> , 1980 [83]	Dynamic therapy= social skills training Psychoeducation= Waiting list Daily psychoeducation = Standard care> Weekly psychoeducation Psychoeducation> Standard care
Family Interventions	Strang <i>et al.</i> , 1981 [112] Glick <i>et al.</i> , 1991, Fallon <i>et al.</i> , 1985 [88, 87] Leff <i>et al.</i> , 1985 [89] Leff <i>et al.</i> , 1989 [90] McFarlane <i>et al.</i> , 1985 [94] Razali <i>et al.</i> , 2000 [113] Schooler <i>et al.</i> , 1997 [95] Tarrier <i>et al.</i> , 1988 [96] Telles <i>et al.</i> , 1995 [97] Xiong <i>et al.</i> , 1994 and Zhang <i>et al.</i> , 1994 [98,99]	Behavioral management> Intensive case management Family intervention = standard care Social interventions = standard care Psychoeducation+family therapy = psychoeducation +relative groups Multiple family psychoeducation= single-family psychoeducation Behavioral intervention+ family psychoeducation> Behavioral intervention Supportive treatment= family management/problem solving Behavioral enactive therapy= behavioral symbolic therapy= psychoeducation= standard care Behavioral management= standard care Psychoeducation+ multiple-family therapy= standard care
Community Interventions	Marshall <i>et al.</i> , 2000, Bond <i>et al.</i> , 1988, 1991; Stein <i>et al.</i> , 1999; Bigelow <i>et al.</i> , 1991; [100, 101,102,106,108] Bush <i>et al.</i> , 1990 [114] Ford <i>et al.</i> , 1995 [103] Modrcin <i>et al.</i> , 1988 [104] Solomon and Draine, 1995 [105] Bond <i>et al.</i> , 1989, Dixon <i>et al.</i> , [107,109] Sands <i>et al.</i> , 1994; Chaan <i>et al.</i> , 1994 [115 and 116]	Assertive community treatment= standard case management Assertive Community Treatment> standard case management Intensive case management> standard case management Strength case management= standard case management Intensive consumer case management= case management Assertive community treatment+ crisis house= assertive community treatment+ purchased housing Assertive community treatment> Intensive case management
Mixed Interventions	Azrin <i>et al.</i> , 1998 [77] Guimon <i>et al.</i> , 1993 [117] Herz <i>et al.</i> , 1996 [110] Hogarty <i>et al.</i> , 1986, 1991 [111, 118] Hogarty <i>et al.</i> , 1997 [84] Hornung <i>et al.</i> , 1996, 1998 and Buchkremer <i>et al.</i> , 1997 [80,81,82] Kelly <i>et al.</i> , 1990 [121] Linszen <i>et al.</i> , 1996 [119] Merinder <i>et al.</i> , 1999 [120]	Patient plus family behavioral intervention= patient behavioral intervention> psychoeducation Patient+family group therapy= standard care Individual plus multifamily groups> standard care Family therapy plus education= socials skills training= family treatment plus social skills training> standard care Personal therapy= family psychoeducation= personal therapy plus family therapy> standard care Psychoeducation= psychoeducation plus cognitive therapy = psychoeducation plus relatives groups= non-specific leisure-time groups In-home behavioral intervention= clinic based behavioral intervention= home and clinic visit> standard of care Individual psychosocial plus behavioral family interventions= individual psychosocial intervention Family and patient psychoeducation= standard care

Individualized Interventions

Based on a systematic review of the literature, Zygmunt *et al.* [66] reported that psychoeducational programs are not effective in increasing adherence, unless they are accompanied by behavioral components, and support services. Instruction in problem-solving, motivational techniques, and individualized interventions aimed at resolving specific problems with adherence may thus be more valuable than general psychoeducational programs alone.

As mentioned earlier, substance abuse is a strong predictor of nonadherence [18], therefore programs aimed at preventing or treating substance abuse disorders may improve adherence with atypical antipsychotic therapy (Table 5).

Table 5. Interventions to Improve Adherence

Fostering good patient-clinician relationships
Selection of an antipsychotic based on prior response and tolerability factors
Adequate monitoring of symptoms and side-effects of medications
Treatment of comorbid substance abuse disorders
Psychoeducation with focus on attitudinal and behavioral interventions (individualized interventions)
Psychoeducation with motivational approaches.
Behavioral strategies (problem solving, self monitoring, cues and reinforcement)
Cognitive techniques and targeted patients attitudes towards medications.
Intensive Case Management
Assertive Community Treatment
Family programs incorporating behavioral techniques.

Family Involvement and Therapeutic Alliance

A close and ongoing relationship with the physician and active involvement of the family, are important in enhancing adherence [9]. In a meta-analysis, Pitschel-Walz *et al.* [67] found that relapse rates decreased by 20% when family members actively participated in treatment, and this effect was particularly strong when family involvement continued for more than 3 months. Even fairly brief educational efforts from family members, can have a positive impact. Cassidy *et al.* [68] found that readmission was significantly less likely when family members participated in an 8-week psycho-educational program. When patients whose family members participated in the program were readmitted, they spent fewer days in the hospital than did those whose family did not participate.

In addition to family involvement, a good relationship between a patient and their physician is essential to developing individualized treatment approaches, which address issues interfering with adherence [24].

CONCLUSIONS

Improving patient adherence to antipsychotic maintenance therapy is crucial to any effort in decreasing rates of relapse and rehospitalization in patients with schizophrenia. Psycho-educational programs, treatment of comorbid substance abuse disorders, family involvement with treatment, and a

good patient-clinician relationship, all contribute to improving adherence. Even with these efforts, patients who cannot tolerate the drug, will be more inclined or motivated to discontinue treatment [69]. Clinicians now have many pharmacologic options to choose, and tolerability should be a key consideration. Overall, the atypical antipsychotics appear to be better tolerated than the conventional agents, but differences in adverse event profiles among the atypical drugs, must be taken into account when reaching a prescribing decision.

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