Facilitating Compliance With Antipsychotic Medication

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Noncompliance with medication is common among patients who have schizophrenia and is a leading cause of rehospitalization in this population. Both standard and subjective risk-factor assessments have been used to identify patients who are likely to refuse or discontinue treatment. Noncompliant patients who have schizophrenia commonly have been treated with potent D_2 dopamine-receptor antagonists and therefore may have experienced extrapyramidal side effects. The newer antipsychotics (i.e., serotonin-dopamine antagonists) are efficacious in reducing the symptoms of schizophrenia without associated dysphoria and motor side effects. Clozapine and other newer antipsychotics may improve certain aspects of cognition. The improved psychiatric state and cognitive function may facilitate "involved compliance" as a result of increased insight, awareness, and judgment. These cognitive faculties allow patients to appreciate their improved state and take steps to maintain it. The periodic visits for blood monitoring mandated for clozapine therapy also facilitate the formation of a therapeutic alliance that allows the clinician to monitor compliance. Facilitating involved compliance this way among patients who have schizophrenia may reduce the cost of this disorder to society.

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Schizophrenia afflicts 1% of the population in the United States, or approximately 2.5 million Americans, but the disorder consumes a disproportionate share of total health expenditures in this nation—approximately $16–23 billion annually by some estimates.[1,2] In addition, noncompliant patients who have schizophrenia account for almost 40% of the national annual cost of rehospitalizations.[3] The prevalence of noncompliance with medication among discharged patients who have schizophrenia is approximately 50% after 1 year and 75% at 2 years.[4]

Prior to the emergence of the newer-generation antipsychotics in the 1990s, noncompliance with oral neuroleptics (primarily of the phenothiazine category) was 46% and for depot neuroleptics was 15% to 20%.[5] Depot neuroleptics have been the preferred therapeutic vehicle for many noncompliant patients, because they provide a method of drug delivery that does not require patients to take pills.[6] Double-blind studies have usually found lower relapse rates in patients treated with depot as opposed to oral agents.

Typical antipsychotics, or dopamine-receptor antagonists, are associated with extrapyramidal syndrome (EPS), an often uncomfortable side effect that manifests as tremor, rigidity, akinesia (or bradykinesia), akathisia, or dystonia. A less overt (though no less debilitating) side effect associated with the typical antipsychotics is neuroleptic dysphoria—a condition characterized by listlessness, tiredness, lack of ambition or interest, and irritability.[7]

Clozapine and the novel antipsychotics risperidone, olanzapine, quetiapine, sertindole, and ziprasidone exhibit more tolerable side effects, with negligible EPS, at initial or moderate dosages.[8–11]

The extent to which serotonin-dopamine ($5\text{-}HT_{2A}$–D_2) receptors are occupied distinguishes dopamine-receptor antagonists from the newer antipsychotics. Whereas typical neuroleptics primarily antagonize dopamine at D_2 receptors, the newer agents may occupy D_2 receptors to a lesser extent and are characterized by equal or greater binding at $5\text{-}HT_{2A}$ sites. D_2 receptors predominate in the basal ganglia and the nigrostriatal system (e.g., caudate, putamen), which mediate motor activity. Antagonism of D_2 receptors in these regions thus culminates in deficits that lead to parkinsonian EPS motor side effects and possibly tardive dyskinesia (TD). A diminished propensity to bind D_2 receptors in the basal ganglia is likely to result in an enhanced side effect profile, with fewer and less severe motor manifestations (i.e., EPS). With improved tolerability and efficacy profiles that are superior to those of typical antipsychotics, the newer antipsychotics may result in improved rates of compliance.[5,8,12]

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DEFINING NONCOMPLIANCE

Compliance generally refers to the degree of conformity between standards of behavior and standards of treatment.[5] Gaebel[5] has characterized specific subtypes of noncompliance, including refusal of treatment, discontinuation of treatment, and irregularities in treatment.

Refusal of treatment can occur during an acute episode as the result of the patient's denial of the illness. Discontinuation of treatment often occurs at discharge, when the patient's behavior is no longer governed by compliance-ensuring procedures on the wards, and the patient feels no more need to continue taking the drug. Taking the medication may be construed as part of a "sickness" role, whereas stopping the medication equates with being well and functioning successfully in the community. Occasionally, a false sense of security or invulnerability overcomes a discharged patient, especially when days, weeks, or even months may lapse without any discernible adverse effects from discontinuation of the medication.[13] Subsequently, however, a relapse ensues, necessitating rehospitalization.

Irregularities of treatment occur as a result of the complexity of the treatment regimen. "Capricious compliance" is one type of irregularity in which patients take varying amounts of their medications on the basis of how they feel on a particular day.[5]

DETECTING NONCOMPLIANCE

Noncompliance can be detected by several means: patient self-report, which is notoriously unreliable; direct observation; pill count, which does not ensure that the prescribed medication actually has been ingested; and biological analyses, including measurement of drug levels in the plasma, saliva, and urine.[5] Tests of saliva and urine have an advantage because they are less invasive than monitoring plasma. The addition of markers such as riboflavin or phenol red to the medication may assist in determining levels of compliance using assays of urine.[14]

RISK FACTORS FOR NONCOMPLIANCE

Weiden and colleagues[4] have classified the assessments of risk factors for noncompliance as standard or subjective; these are summarized in Table 1.

Table 1. Risk Factors for Noncompliance*

Standard Assessments	Subjective Assessments
Anxiety	Lack of insight
Grandiosity	Denial of illness
Depression	Unsupportive family belief
Medication side effects	Negative perception of illness
Forgetfulness	Quality of physician-patient relationships
Comorbid substance abuse	Benefits versus risks of medication
Lack of outpatient contact	

*Based on Weiden et al.[4]

Standard Assessments

The intrinsic complexity of the therapeutic regimen is a major contributing factor in noncompliance. Conversely, simplicity of treatment is a major contributing factor in compliance. A behavioral structure that includes continuous care, a supportive level of supervision, and environmental security positively influences a patient's compliance with the therapeutic regimen. Social isolation and states of anxiety, paranoid delusions, depression, medication complexity, and medication side effects, on the other hand, elevate the risk of noncompliance.[14–16] In one study of 29 patients with schizophrenia who habitually refused to take medication and 30 patients with schizophrenia who complied with medication, Van Putten and coworkers[17] found that noncompliance with antipsychotic medication was associated with a resurgence of an ego-syntonic grandiose psychosis, whereas habitual compliance was associated with decompensations, including depression and anxiety. These findings suggested that some patients who have schizophrenia may prefer a state of ego-syntonic grandiosity to one of drug-induced normality.[17]

Other standard factors that favor noncompliance are the patient's level of forgetfulness, in the context of the cognitive disorganization to which patients who have schizophrenia are prone,[18] as well as the presence of negative effects of the medication[14,19] and increased severity of symptoms.[14] Moreover, patients who have treatment-resistant schizophrenia are at high risk for noncompliance: The lack of efficacy of antipsychotic treatment and its accompanying intolerable side effects predispose these patients to forgo their medication.

Concurrent substance abuse also increases the risk of noncompliance.[20–22] In this context, Owen and coworkers[23] reported that the combination of substance abuse, noncompliance with medication, and lack of contact by outpatients led to notably greater severity of symptoms, and this triad tended to define a particularly high-risk group of patients who have schizophrenia.

Subjective Assessments

Subjective risk-factor assessments for noncompliance with medication include lack of insight, denial of the illness, and adverse family beliefs concerning the value of medication.[4] Budd and colleagues[23] have identified 3 pivotal factors that can predict compliance: First, patients must view themselves as vulnerable to the illness (i.e., susceptibility); second, they must perceive that the illness is severe (i.e., severity); and third, they must be convinced of the effectiveness of the proposed treatment regimen (i.e., benefits).

Smith and associates[24] demonstrated the benefit of the patient's having supportive family members. Patients with schizophrenia whose family members or significant others had insight exhibited improved compliance; under these circumstances, patients who had actively involved families also tended to be more aware of their illness.

Other, less tangible subjective factors that have a negative bearing on compliance with medication include the stigma attached to the illness,[25] the quality of the physician-patient relationship,[26] the perceived benefit of the medication,[27] and perceived distress from side effects.[28] The quality of the therapeutic alliance between patient, physician, and other allied health workers is crucial to compliance. Thus, modifying negative views of the health care team might tend to promote compliance. Despite denying their illness, patients who trust their clinicians and believe that they sincerely wish to help may be more likely to take medication.

THE ROLE OF COGNITION IN COMPLIANCE

Noncompliance with medication is widespread in schizophrenia, partially as a result of the cognitive deficits that are a hallmark of the disease and that affect insight, awareness, and judgment.[29] Attention, memory, abstract problem-solving, and other processing functions are compromised in schizophrenia and are compounded by positive symptoms such as hallucinations and paranoid delusions.[30]

Cuffel and colleagues[31] cited findings from two independent multinational trials[32,33] that estimated that poor insight figures prominently in more than 80% of patients who have schizophrenia. On the other hand, patients with schizophrenia who have greater awareness perceived a heightened need for outpatient treatment, and they demonstrated improved compliance to therapy when their levels of compliance and awareness were measured concurrently.[31]

Atkinson's group[34] underscored the value of education in supporting compliance: Even patients who have schizophrenia can learn and comprehend information that is relevant to their illness. Several studies have reported on the salutary effect of education on compliance, particularly that of educational programs that teach patients about the prodromal warning signs of relapse and the effects of medication.[35] In chronically ill patients, pharmacotherapeutic improvement of cognitive function is a prerequisite to such psychoeducational augmentation.

In addition, the superior efficacy of the newer antipsychotics in treating both the positive and negative symptoms of schizophrenia—without the intolerable side effects of EPS—results in an improvement in subjective well-being that is more conducive to compliance.[8,9]

INVOLVED COMPLIANCE WITH NEW-GENERATION ANTIPSYCHOTICS

The use of depot antipsychotics often provides a useful tool for patients who may be poor pill takers. The newer antipsychotics may provide an alternative by inducing "involved compliance." Involved compliance presupposes an awareness of illness, a capacity to contrast pretherapeutic and posttherapeutic well-being, and an ability to realize that posttherapeutic improvement in psychiatric state is contingent on maintenance of the therapeutic regimen.

Clozapine

By some estimates, between 30% and 61% of patients who were previously unresponsive to typical neuroleptics derive clinically significant advantages from treatment with clozapine.[36] Clozapine is indicated for use in patients who have chronic schizophrenia (a population at high risk for noncompliance) who prove to be either refractory to typical neuroleptics or intolerant to those drugs, suffering side effects such as EPS or TD.[9,37] Reports are lacking that treatment with clozapine causes TD[37,38]; in fact, clinical reports suggest that clozapine actually can suppress TD.[39–41] The restricted use of clozapine for treatment-resistant patients who have schizophrenia is the result of an associated risk of agranulocytosis (currently reported to be 0.38%),[42] which mandates frequent monitoring of blood. In fact, the therapeutic alliance that results from the need for this safety measure is believed by some to augment clozapine's efficacy in improving psychiatric symptoms and is conducive to involved compliance.

In a comparative study with chlorpromazine, Claghorn and associates[12] demonstrated that treatment with clozapine in psychotic inpatients resulted in significantly fewer discontinuations as a result of adverse events: 24% of chlorpromazine-treated patients, compared with 8% of clozapine-treated patients. These figures thus indicate a better rate of compliance among the clozapine-treated patients. Of the chlorpromazine-treated patients who discontinued medication in this study, almost 60% did so because of severe EPS.[12]

Involved compliance may be attained by patients who have schizophrenia by means of therapy that is directed at enhancing their cognitive function. Menditto et al.[43] suggested that, in comparison with patients who had chronic schizophrenia treated with dopamine-receptor antagonists, patients given clozapine exhibited improved responses in rehabilitation programs. A number of studies have shown that, overall, clozapine enhances cognitive functioning. Clozapine improves attention, response speed, verbal fluency, and recall memory,[44-49] although improvement in executive function and short-term memory appears to be lacking.[44,46]

In reviewing data on both efficacy and tolerability, Meltzer[44] identified clozapine-induced changes that tend to

promote compliance: improvements in psychopathologic characteristics, cognitive function, side effect profile (with minimal EPS), together with a low rate of rehospitalization.

Risperidone and Other Novel Antipsychotics

A double-blind study of risperidone and haloperidol that assessed verbal working memory showed that under both distracting and nondistracting conditions, risperidone-treated patients demonstrated greater improvement with both fixed and flexible dosing regimens.[50] In addition, risperidone has been shown to improve selective attention and alertness.[51] Although risperidone has been shown to be associated with some dose-dependent EPS,[52,53] most patients can be treated with doses that cause negligible EPS; the findings of improved cognitive functioning suggest that risperidone is more likely than conventional antipsychotics to facilitate involved compliance.

Similar studies assessing the effects of olanzapine, quetiapine, or ziprasidone on specific cognitive measures are lacking to date. Nonetheless, by and large, the tolerable side effect profile of the newer-generation antipsychotics and their superior efficacy to the typical antipsychotics indicate a promising prognosis toward involved compliance.

THE COST OF NONCOMPLIANCE WITH MEDICATION

Weiden and Olfson[3] estimated the national annual cost of rehospitalization for patients who have multiple-episode schizophrenia, focusing on the burdens of cost that are attributable to lost efficacy of medication and diminished compliance with medication regimens. These investigators reported that 60% of the costs of rehospitalization were attributed to lost efficacy and 40% to noncompliance, the postdischarge frequency of which was 7.6% per month. Among 257,446 patients with multiple-episode schizophrenia who were discharged from inpatient settings in the United States in 1986, the aggregate cost of readmission approached $2 billion. These data suggest that substantial cost savings could be realized with improved pharmacotherapeutic and psychosocial approaches to managing noncompliance.

The cost-effectiveness of pharmacotherapy is germane to a discussion of compliance for two central reasons. First, the cost of medication is one of the factors that patients take into account when deciding whether to comply with medication regimens, although Budd and colleagues[23] found cost to be less important in determining compliance than were the patients' perceptions of their susceptibility to the illness, its severity, and the benefits of the treatment. Second, in a paradigm that has shifted toward managed care, physicians are accountable to the government, industry, and other third-party payors for the cost-effectiveness of therapies.

A recent double-blind study[54] that compared clozapine (N = 205) with haloperidol (N = 218) in treatment-refractory schizophrenia showed that 57% of clozapine-treated patients continued taking their medication for the entire year, compared with only 28% of haloperidol-treated patients, indicating a significant advantage in the rate of compliance among patients given clozapine compared with those given haloperidol ($p < .001$). Clozapine-treated patients experienced less EPS and no TD and had fewer mean days of hospitalization than did those treated with haloperidol—143.8 versus 168.1 days, respectively ($p = .03$). The total per capita costs to society were $58,151 in the clozapine-treated group and $60,885 in the haloperidol-treated group, a savings of nearly $3000 per year with clozapine.[54] Honigfeld and Patin[55] indicated that cost savings tend to be even higher during the second year of treatment with clozapine because of the change from expensive inpatient facilities to less costly community settings. Because noncompliance is the most common cause of relapse, improving compliance saves on costs of hospitalization as well as outpatient rehabilitation.

Treatment with risperidone also results in a reduction of days of hospitalization in patients who have chronic schizophrenia.[56] Likewise, treatment with olanzapine results in a lower total cost of health care than treatment with haloperidol.[57] On the basis of acquisition costs, the newer antipsychotics tend to be more expensive than the typical antipsychotics, but, because of the superior efficacy and lower rate of hospitalization associated with these novel agents, they are cost-effective.

CONCLUSIONS

The increased efficacy and more tolerable side effect profile of the newer, atypical antipsychotics relative to those of the conventional antipsychotics enhance the psychiatric well-being of individuals with schizophrenia who take these newer medications. In addition to controlling both the positive and negative symptoms of the illness, clozapine and some of the novel antipsychotics enhance cognitive function, a therapeutic benefit that improves insight, awareness, and judgment, factors that are crucial to attaining "involved compliance" and subsequently preventing relapse. Prolonging remission of the illness through compliance with medication regimens limits hospital stays, improves the patient's quality of life, and cuts down on the indirect costs of the illness (e.g., costs associated with persistent aggression). Thus, the therapeutic benefits acquired through the use of newer-generation antipsychotics eventually translate to a long-term cost benefit.

Drug names: clozapine (Clozaril), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), sertindole (Serlect).

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