

EFFICACY VERSUS RISK IN MODERN TREATMENT OF SCHIZOPHRENIA

Ovidiu ALEXINSCHI, Gheorghe NEDELCIUC, Lăcrămioara FĂRCĂȘEL

Abstract:

The multidimensional negative symptom domain of schizophrenia remains one of the most challenging aspects of the treatment of this disorder. While mixed findings suggest a role for second-generation antipsychotics, the development of novel therapeutic approaches that target cognitive impairments and negative symptoms are being actively pursued. Until newer agents become available, clinicians should seek to optimize treatment of positive symptoms and depressive symptoms, and reduce medication side effects that may contribute to negative symptom severity, and increase the use of established behavioural approaches, such as social skills training, that have been demonstrated to improve psychosocial functioning. In this article we tried a review of the most recent findings and approaches of the pharmacological therapy for schizophrenia.

KEYWORDS: second generation antipsychotics, target cognitive impairment, multidimensional negative symptoms.

Nonadherence with antipsychotic medications is a leading source of preventable morbidity in the community treatment of schizophrenia.^[1] Approximately one-third of patients with schizophrenia are noncompliant with their prescribed medication regimen.^[2] These patients are at increased risk of symptom exacerbation^[3] and inpatient readmission.^[4] Missing as few as 1-10 days of oral antipsychotic therapy nearly doubles the risk of hospitalization.^[5] Clinical research and expert opinion^[6] support the use of depot antipsychotics as a maintenance treatment for patients with a history of nonadherence with oral antipsychotics. However, in the United States, long-acting antipsychotic medications are only prescribed to between 19% and 30% of patients with known recent medication nonadherence.^[2,7]

Although a number of single-site clinical studies have shown that use of depot antipsychotics varies by patient race/ethnicity and age,^[7] no US study has examined the impact of the broad range of patient, physician, and treatment setting characteristics. In light of evidence that substantial numbers of patients with known medication nonadherence who might benefit from depot antipsychotic medications are not receiving this treatment, we sought to examine correlates of depot use among recently medication nonadherent patients with schizophrenia. A greater understanding of the pattern and distribution of depot antipsychotic use may help to target initiatives aimed at improving use of depot preparations. A study was conducted to assess patient, physician, treatment, and setting factors that might influence the decision to initiate depot antipsychotic medications for outpatients with schizophrenia and recent medication nonadherence. Prior to conducting this study, we hypothesized that depot antipsychotic use would be preferentially prescribed to patients with the most pervasive, persistent, and consequential medication nonadherence and to patients with fewer social supports such as those who were living alone or those with little family contact.

In outpatient psychiatric practice, psychiatrists use long-acting antipsychotic injections to manage fewer than 1 in 5 patients with schizophrenia having episodes of medication nonadherence. Although consideration of long-acting antipsychotic injections is recommended for patients with a

history of problems with adherence on oral medication,^[6] most patients in this nationally representative community sample who were not adherent with oral antipsychotic medications were not prescribed long-acting antipsychotic injections. The relatively low rate of use is broadly consistent with previous research.^[2,7]

The clinical decision to initiate injection antipsychotic medications appears to rest on a clinical assessment of the risks and consequences of poor medication adherence. Patients at greater risk, specifically those who have a history of persistent nonadherence and those admitted for inpatient care during their last episode of nonadherence, were more likely to be started on injections. However, some patient groups at high risk for recurrent medication nonadherence, such as patients who live alone and younger patients,^[1] had surprisingly low levels of injection use.

Depot antipsychotic medications are not widely used beyond those who are publicly insured or treated in residential or inpatient facilities. These settings presumably have staff members to facilitate delivery of depot antipsychotics and cater to the more severely ill. Innovative strategies to train more psychiatrists and their staff in the use of depot antipsychotics may help promote their use in different settings and in patients who are less severely ill but are still medication nonadherent. In general, adoption of technologies that vary from current or typical practices face significantly greater challenges in diffusing into practice, than those that rely on existing practices.^[8] For this reason, greater opportunities for first-hand observation and hands-on training may be needed. One approach is to set up specialty long-acting antipsychotic injection clinics in private and public outpatient settings that accept referrals. Mobile outreach services provide another option for delivering long-acting injections.^[9] Use of long-acting antipsychotic medications was uncommon among patients prescribed antidepressants or mood stabilizers just prior to the start of the last episode of antipsychotic nonadherence. Some psychiatrists may perceive that the marginal benefit of a long-acting antipsychotic injection is diminished when it does not obviate the need for oral medications as is the case when several classes of oral psychotropic medications are prescribed. In light of the frequency with which schizophrenia patients receive complex regimens involving oral medications other than antipsychotic medications,^[10,11] this diminishing benefit of depot medications may also hinder use of newer long-acting antipsychotic preparations.

Cognitive impairment has been linked to treatment nonadherence among psychotic patients (review).^[12] Although cognitively impaired patients may have a limited ability to take oral medications on their own, patients assessed as having lower than average intelligence were (after controlling for several potential confounds) significantly less likely to receive depot antipsychotic medications than were those of at least average intelligence. These results suggest that efforts are needed to improve access of depot antipsychotic medications to cognitively impaired patients.

In many but not all health care contexts,^[13-16] patients with private insurance enjoy greater access to evidence-based treatments than publicly insured patients. For long-acting antipsychotics, patients with private insurance were less likely than publicly insured patients to receive treatment. This may reflect greater access to long-acting injections in organized treatment settings than in office-based settings favoured by privately insured patients or a stronger preference for oral second-generation antipsychotics among privately insured patients. With the availability of long-acting injectable risperidone, the difference in rate of use by publicly and privately insured patients may narrow.

Psychiatrists who were more optimistic about the effectiveness of managing medication nonadherence were more likely to treat their patients with depot antipsychotics. Psychiatrists who prescribe injections may have had more opportunities to observe favourable patient outcomes than do psychiatrists who do not prescribe these preparations.^[17] In this study, greater knowledge of depot medications was in turn related to more favourable attitudes toward these medications. Consequently, educational efforts to expand use of depot antipsychotics might be preferentially targeted to psychiatrist groups with low rates of use.

The use of depot antipsychotic medications was not significantly related to patient age, gender, or race/ethnicity. Previous studies of psychotic patients that are not selected for recent medication nonadherence have reported that use of depot antipsychotic medications is significantly more common among males,^[18,19] African Americans,^[18-21] and younger patients.^[22] Because these

demographic characteristics also increase the risk of antipsychotic medication nonadherence (reviews),^[1,24] it is perhaps not surprising that they are not significantly related to depot antipsychotic use among patients selected for recent medication nonadherence.

With the introduction of injectable long-acting risperidone, it will be important to track the extent to which patients and psychiatrists become more willing to utilize depot preparations and to assess changes in factors that influence these decisions. Early clinical research indicates that medication nonadherence with oral antipsychotic medications is the most common reason for initiating risperidone long-acting injections,^[26-29] that poor prior antipsychotic adherence predicts greater improvement on risperidone long-acting injections,^[29] and that patients who are switched from another depot are much less likely to discontinue risperidone long-acting injections than those switched from oral antipsychotic medications. These findings suggest that factors which have influenced use of the older depot antipsychotic medications may continue to play a role in medication management decisions with the newer injectable antipsychotic preparations.

Several longitudinal observational trials are underway in Europe with patients with schizophrenia receiving risperidone microspheres. By the way, in Europe, risperidone microspheres are available at a dose of 75 mg as well as in doses of 12.5, 25, and 50 mg, which are available in the United States. Having said that, practice in Europe is similar to practice in North America. A research poster presented data on the effectiveness of switching people with schizophrenia to long-acting risperidone microspheres early in their illness.^[30] They were not quite first-episode patients, but they were not chronic patients. The investigators found that the injectable agent was acceptable by this patient population, and the relapse rate at 6 months was 28%, which is good for such patients.

This is an interim report of a continuing multicenter trial in Belgium. The researchers reported on 61 subjects who had been followed for up to 6 months. The mean subject age was 31.7 years, and enrolment criteria included a documented history of fewer than 4 psychotic episodes. Long-acting preparations have tended to be reserved for patients late in their course of illness, when they become treatment resistant. The importance of this trial with long-acting risperidone, and I think this can be generalized to any long-acting SGA, is that it is acceptable to administer early in the course of illness. It provides the efficacy, relapse prevention, and improvement in symptoms over time that you see with other antipsychotics. The problem in this study is the lack of a group treated with a comparator. The reader is left to guess, but based on my knowledge of how early episode patients respond, it looks like the response we would expect from an effective antipsychotic. I think, however, that the take-home message is more about acceptability of the depot medication in this population than about efficacy per se.

In another study, 849 patients were randomized to flexible dosing by a clinician.^[31] They received either 25-mg, 50-mg, or 100-mg equivalents for 9 weeks. Following this, they received a fixed dose for 12 weeks, and then the 410 subjects who remained in the study entered a maintenance phase, in which they were randomized to placebo or active treatment for 24 weeks. This study was a hybrid of dose-finding and relapse prevention. And it appears that paliperidone palmitate will be an effective medication in terms of relapse prevention; it separated out from placebo quite quickly. One can argue about whether risperidone or paliperidone is better, given that paliperidone is a metabolite of risperidone. Let's just bypass that argument and ask the question, what are the potential advantages of paliperidone palmitate over risperidone microspheres? One is that paliperidone palmitate is administered every 4 weeks, whereas risperidone microspheres are administered every 2 weeks. The second is that paliperidone palmitate will not need refrigeration, so it will be convenient for the clinician to store on site.

I'd like to mention that some pharmacokinetic studies were presented that examined whether long-acting paliperidone and risperidone can be injected into the deltoid muscle.^[31] It's presently an off-label use of risperidone microspheres, but it appears that the pharmacokinetics might permit deltoid injection.

Another new antipsychotic is loperidone, a mixed dopamine D2, serotonin 5-HT_{2A} antagonist, a member of the "done" family, including risperidone and ziprasidone. It's still a different

antipsychotic from those; it has a high affinity for 5-HT_{2A} and adrenergic alpha-1 receptors and low affinity for serotonin 5-HT_{1A}, dopamine D-1, and histamine receptors.^[33] Iloperidone had an active phase 3 clinical trial program in the late 90s when it was owned by Novartis. It is now owned by Vanda, which has done another phase 3 pivotal trial comparing iloperidone with placebo and, as an active comparator, with ziprasidone.^[33] The data are under review by the FDA, and the drug may be approved as early as this summer or fall. The interesting fact is that a long-acting version of the medication has been developed, which is unusual for an antipsychotic before its initial FDA approval. A microsphere formulation was tested for safety and pharmacokinetics during 2000 to 2002. If the oral version gains FDA approval, it would not take much time to proceed with phase 3 trials for the injection. A long-acting injectable form of iloperidone may be available within the near term. In the open-label trial presented at the APA conference that was based on data from 2002, 64 subjects received oral iloperidone for 21 days; 20 received placebo.^[34] The patients then received at least 2 cycles of injections every 28 days. The depot formulation appeared safe and well tolerated. If approved, iloperidone will have the advantage of being a 4-week medication. It would clearly need to go through extensive phase 3 testing, but having it already in a depot formulation with some safety data is very promising because that tends to be the Achilles heel of this development process. Many antipsychotic agents aren't amenable to depot formulation. The difficulty of this process is illustrated by long-acting olanzapine, which was recently disapproved by the FDA because it caused intense sedation.

Nowadays, the big news is that at least 2 long-acting SGAs that can be given in 28-day cycles are in testing and may be clinically available in the next few years. A recent literature review found no convincing evidence to support or disprove the efficacy of antidepressant treatment for depressive symptoms in adults with schizophrenia.^[35] Evidence for an augmenting effect of mood stabilizers in the antipsychotic treatment of schizophrenia is similarly mixed.^[36,37] Given that concurrent medication administration increases the risk of adverse drug reactions,^[38] efforts to reduce psychotropic coprescription might help improve tolerability and adherence of antipsychotic medications.^[44] Treatment with mood stabilizers was significantly less common among patients during treatment with LAR than during treatment with FD or HD. It is possible that this difference reflects inherent mood stabilizing properties of risperidone^[39,40] or less mood instability in patients selected for LAR therapy.

Following discontinuation of long-acting antipsychotic medications, most patients continue to receive oral antipsychotic medications. This suggests that problems with continuity of long-acting injection medications do not necessarily generalize to patient rejection of oral antipsychotic medications. A longer period of follow-up after discontinuation of long-acting antipsychotic medications would permit a more complete assessment of the frequency with which these patients are restarted on long-acting medications. Patients with schizophrenia who initiate long-acting antipsychotic injections commonly exhibit evidence of nonadherence with oral antipsychotic medications in the months before their first injection. Treatment with long-acting antipsychotic medications is often brief, usually lasting no longer than 7-10 weeks. Detailed clinical research is needed to determine the role of medication-related factors, such as dosing, tolerability, and efficacy, as well as other key clinical and psychosocial factors that contribute to the early discontinuation of depot antipsychotic medications. More importantly, research is needed to develop intervention strategies that will enhance the continuity of depot antipsychotic therapy in community treatment.

Relatively few treatments exist for the very problematic domain of signs and symptoms of schizophrenia called 'negative symptoms'. Features such as emotional blunting and lack of outward emotional display have long been considered fundamental symptoms of schizophrenia, and the 'negative symptom' terminology refers to a decrease or loss of normal functions, such as a loss of energy, motivation, and emotional display of affect.^[41] Negative symptoms may be more stable than positive symptoms, and commonly begin to emerge very early in the course of schizophrenia, even before the development of positive symptoms. In fact, negative symptoms often first appear during the prodromal, or even premorbid, phase of schizophrenia. Negative symptoms are strongly associated with quality of life and social and occupational functioning.^[42]

Although the second-generation, or 'atypical,' antipsychotic agents may not be substantially more effective than first-generation or 'conventional' agents in the treatment of positive symptoms (except for clozapine, which is typically reserved for treatment-resistant schizophrenia), some evidence suggests that newer agents may better improve, or contribute less to the secondary worsening of, negative symptoms and/or cognitive impairments.^[43] Most studies on this issue have been carried out in acutely ill patients who demonstrate improvements in positive symptoms, negative symptoms, and other areas, such as mood and anxiety, suggesting that negative symptom improvements may be in part secondary to other improvements.^[44] While it remains less clear whether second-generation agents treat primary negative symptoms, they tend to work better than first-generation agents on negative symptom ratings, at least in part related to higher rates of EPS and related secondary negative symptoms induced by first-generation treatment in those trials. There is some evidence that serotonin-specific reuptake inhibitors may be modestly helpful in managing negative symptoms. Further research on the effects of agents acting on the glutamate system, including glycine and d-cycloserine, is required in light of the mixed results to date. Negative symptoms are correlated with neurocognitive impairments, and given recent increasing interest in pharmacologic agents that may be cognitive enhancers, some of these medications may hold promise for the treatment of negative symptoms.

The most recent results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), published in March 2007,^[45] indicate that patients' psychosocial improvement was modest no matter which medication they received during the 18 months of observation. The Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS)^[46] from Britain also found that the type of antipsychotic medication was not all that important for outcome. These 2 effectiveness studies have caused some confusion because they suggest that there are few differences in effectiveness between the first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs). However, there are variables in the studies that may modify that conclusion. In CATIE, for instance, the objective was to compare FGAs with SGAs and to compare SGAs with each other. But unfortunately, for ethical reasons, investigators did not expose patients with tardive dyskinesia to an FGA. Tardive dyskinesia is a severe extrapyramidal side effect (EPS) that develops in patients who usually first have acute EPS. The 231 subjects with tardive dyskinesia represented the patients with chronic schizophrenia who are most vulnerable to acute EPS, and clinicians often choose SGAs precisely to avoid EPS. In CATIE, we missed the opportunity -- for understandable, ethical reasons -- to learn whether, during an 18-month period, patients with tardive dyskinesia randomly assigned to an FGA or an SGA would have fared differently in terms of acute movement disorders, intolerability, rates of discontinuation, and treatment response. In these patients, investigators could only compare the SGAs among themselves. The patients with tardive dyskinesia were different in other ways from the other patients: they had significantly more substance abuse and a higher severity of illness as measured by the Positive and Negative Syndrome Scale (PANSS). By assigning them only to SGAs, investigators also missed the opportunity to examine the differential response of patients with severe illness and concurrent substance-use disorders to old and new drugs.

CUtLASS was different. Many of its patients took FGAs and often received them as depot injections, unlike CATIE in which more patients took SGAs. The CUtLASS study had flaws, including the fact that sulpiride, which many patients took, was considered to be an FGA. Quite a few psychiatrists consider sulpiride to be an SGA.

Recurrent relapses are neurotoxic and may account for the deteriorating course of patients with schizophrenia.^[47] It is of utmost importance to help patients with schizophrenia stay on their medications and avoid relapse. In community and outpatient settings, 70%-80% of patients are either partially or totally noncompliant.^[48] This is unacceptable if the goal is to achieve recovery. Patients with schizophrenia would have much better outcomes than we usually achieve if they were protected from relapses by ensuring treatment adherence from the first episode. But we have no study of first-episode patients assigned to a guaranteed-adherence regimen, which would be depot medication, vs treatment as usual with oral medication.

The FGA depot medications do protect against relapse; however, they do not appear to restore the patient's functioning over time. A confounder in looking at outcomes with FGA depot medications is that we have tended to use them in the patients who have had repeated relapses, [which is] an unrepresentative group of patients who have already deteriorated, who lead chaotic lives, and who likely have substance abuse, poor insight, cognitive deficits, and low motivation. These difficult patients, the 5%-10% who, during the past 30 years, received haloperidol decanoate or fluphenazine decanoate, do not represent the possible outcome of patients who might receive depot medication early in the course of illness. Clinicians were reluctant to use injectable FGAs because of concern about tardive dyskinesia, but the oral FGAs have the same risk. So we never learned, even though these depot FGAs have been around for 30 years, much about their efficacy in the average patient except in some small studies in which the injectable form was superior to the oral form of the same medication. They do protect relapse better than the oral medication.^[49]

We also have a couple of new formulations. One of them may be considered a new drug, which is paliperidone, or 9-hydroxy risperidone, an active metabolite of risperidone. At first blush, it looks like the same drug, but it behaves differently and is in a special formulation. It has minimal requirements for cytochrome oxidation and is excreted directly by the kidney, unlike risperidone, which is oxidized completely. This offers an advantage for patients with advanced liver disease, severe alcoholism, or hepatitis. Moreover, paliperidone does not compete for metabolism with other medications that another physician may prescribe, and it causes no cytochrome inhibition or induction that could lead to drug interactions. A third advantage is the osmotic release oral delivery system (OROS) technology that enables paliperidone to be released slowly during its transit through the gastrointestinal tract, which means fewer side effects because of the gradual rise in blood level. The recommended dose is 6 mg starting from day 1 – no need to titrate, and in my opinion, patients get better somewhat quicker.

The other product coming to market is quetiapine extended-release. Quetiapine is not a new drug, but the slow-release formulation will enable clinicians to use doses of 300, 600, or 900 mg once a day, which may improve compliance because regular quetiapine is taken twice daily. A drug that may be marketed later this year is bifeprunox, a partial D-2 agonist like aripiprazole. It doesn't yet have a trade name and is a joint venture of Solvay and Wyeth. Its advantage is a good metabolic profile, with minimal weight gain and minimal serum lipid and glucose elevations.

No new-mechanism drugs are coming to market. Researchers are frantically working to understand the glutamate pathways, and especially the N-methyl-D-aspartate (NMDA) receptor, which we highly suspect is involved in schizophrenia. But we do not yet have any breakthroughs.

On the other hand, an expert review of John M. Kane, Professor of Psychiatry, Neurology, and Neuroscience at Albert Einstein College of Medicine says that Clozapine remains the only medication that has shown consistent superiority over other antipsychotic drugs in the management of patients who fail to benefit adequately from standard treatment. Estimates are that at least one third of patients do not respond adequately to antipsychotic treatment. Of course, these estimates of response rates depend on how response is defined. The majority of patients will improve on antipsychotic medication; however, the definition of treatment resistance usually involves significant psychopathology, eg, ratings of moderate or greater on 2 psychotic symptoms. At the same time, it has been shown that even patients with only 1 psychotic symptom at a moderate or greater level who have failed to show further improvement after taking at least 2 different antipsychotic medications are more likely to benefit from clozapine than from other medications. Clozapine is not an easy medication to use, and it is associated with a variety of side effects. Therefore, considerations around its use should be informed by a clear benefit-to-risk assessment and thorough discussion with the patients and their significant others. Most experts agree that at least 2 antipsychotics should be tried before going on to clozapine. At present there is no real consensus as to whether one of those medications should be a conventional antipsychotic. Therefore, I do not believe that anyone would be faulted for only trying atypical medications prior to taking clozapine. On the basis of data from clinical trials and meta-analyses, olanzapine and risperidone are the 2 medications that have the most data suggesting some superiority over conventional medications, so

it would make sense that at least 1 of those medications is prescribed in an adequate trial before considering clozapine. The duration of an adequate trial is another component of this decision-making process. Most would agree that 6 weeks at an adequate dose is sufficient. Another caveat in this discussion is the issue of compliance. It is important that nonadherence be ruled out as a potential cause of poor treatment response. In addition, the diagnosis and the potential presence of comorbid medical or psychiatric conditions should be reevaluated before considering a patient to be treatment refractory. If the decision is made to institute a trial of clozapine, it is important to monitor for side effects but also to carefully evaluate treatment response. If no improvement is observed after 12 weeks despite an adequate dose of clozapine (500 mg if tolerated), further improvement is unlikely. If, on the other hand, some improvement is observed, further gradual improvement may occur. In those patients who have failed to respond despite an apparently adequate dose, a blood level should be obtained to determine whether or not it is in the therapeutic range. Unfortunately, many patients who might benefit from clozapine are not given a trial – and even among those who are, it is often far later in the illness course than is appropriate.

In summary, the multidimensional negative symptom domain of schizophrenia remains one of the most challenging aspects of the treatment of this disorder. While mixed findings suggest a role for second-generation antipsychotics, the development of novel therapeutic approaches that target cognitive impairments and negative symptoms are being actively pursued. Until newer agents become available, clinicians should seek to optimize treatment of positive symptoms and depressive symptoms, and reduce medication side effects that may contribute to negative symptom severity, and increase the use of established behavioural approaches, such as social skills training, that have been demonstrated to improve psychosocial functioning.

REFERENCES

1. Fenton, W.S., Blyler, C.R., Heinssen, R.K., *Determinants of medication compliance in schizophrenia: empirical and clinical findings*, Schizophr Bull (1997) 23::637-651
2. West, J.C., Wilk, J.E., Olfson, M., et al., *Patterns and quality of treatment for patients with schizophrenia in routine psychiatric practice*, Psychiatr Serv (2005) 283-291
3. Robinson, D., Woerner, M.G., Alvir, J.M., et al., *Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder*, Arch Gen Psychiatry (1999) 56::241-247
4. Svarstad, B.L., Shireman, T.I., Sweeney, J.K., *Using drug claims data to assess the relationship of medication adherence with hospitalization and costs*, Psychiatr Serv (2001) 52::805-811
5. Weiden, P.J., Kozma, C., Grogg, A., Locklear, J., *Partial compliance and risk of rehospitalization among California Medicaid patients with schizophrenia*, Psychiatr Serv (2004) 55::886-891
6. Lehman, A.F., Kreyenbuhl, J., Buchanan, R.W. et al., *The schizophrenia patient outcomes research team (PORT): update treatment recommendations*, 2003, Schizophr Bull (2004) 30::193-217
7. Valenstein, M., Copeland, L.A., Owne, R., Blow, F.C., Visnic, S., *Adherence assessments and the use of depot antipsychotics in patients with schizophrenia*, J Clin Psychiatry (2001) 62::545-551
8. Berwick, D.M., *Disseminating innovations in health care*, JAMA (2003) 289::1969-1975
9. Ferris L.E., De Siato, C., Sandercock, J., Williams, J.I., Shulman, K.I., Working Group: a descriptive analysis of two mobile crisis programs for clients with severe mental illness, *Can J Public Health* (2003) 94::233-237
10. Glick, ID, Pham, D., Davis, J.M., *Concomitant medications may not improve outcome of antipsychotic monotherapy for stabilized patients with nonacute schizophrenia*, J Clin Psychiatry (2006) 67::1261-1265
11. Magliano, L., Fiorillo, A., Guarneri, M., et al., *The National Mental Health Project Working Group: prescription of psychotropic drugs to patients with schizophrenia: an Italian national survey*, Eur J Clin Pharmacol (2004) 60::513-522
12. Nose, M., Barbui, C., Tansella, M., *How often do patients with psychosis fail to adhere to treatment programmes? A systematic review*, Psychol Med (2003) 33::1149-1160
13. Wang, E.C., Choe, M.C., Meara, J.G., Koempel, J.A., *Inequality of access to surgical specialty health care: why children with government-funded insurance have less access than those with private insurance in Southern California*, Pediatrics (2004) 114::584-590
14. Olfson, M., Marcus, S., Sackeim, H.A., Thompson, J., Pincus, H.A., *Use of ECT for the inpatient treatment of recurrent major depression*, Am J Psychiatry (1998) 155::22-29
15. Seldon, T.M., Hudson, J.L., *Access to care and utilization among children: estimating the effects of public and private coverage*, Med Care (2006) 44::((suppl 5)):I19-26
16. Rice, T., Laverreda, S.A., Ponce, N.A., Brown, R.E., *The impact of private and public health insurance on medication use for adults with chronic diseases*, Med Care Res Rev (2005) 62::231-249

17. Olfson, M., Marcus, S.C., Wilk, J., West, J.C., *Awareness of illness and nonadherence to antipsychotic medications among persons with schizophrenia*, Psychiatr Serv (2006) 57::205-211
18. Citrome, L., Levine, J., Allingham, B., *Utilization of depot neuroleptic medication in psychiatric inpatients*, Psychopharmacol Bull (1996) 32::321-326
19. Mark, T.L., Palmer, L.A., Russo, P.A., Vasey, L., *Examination of treatment pattern differences by race*, Ment Health Serv Res (2003) 5::241-250
20. Arnold, L.M., Strakowski, SM, Schwiers, ML, et al., *Sex, ethnicity, and antipsychotic medication use inpatients with psychosis*, Schizophr Res (2004) 66::169-175
21. Kreyenbuhl, J., Zito, J.M., Buchanan, R.W., Soeken, K.L., Lehman, A.F., *Racial disparity in the pharmacological management of schizophrenia*, Schizophr Bull (2003) 29::183-193
22. Price, N., Glazer, W., Margenstern, H., *Demographic predictors of the use of injectable versus oral antipsychotic medications in outpatients*, Am J Psychiatry (1985) 142::1491-1492
23. Perkins, D.O., *Predictors of noncompliance in patients with schizophrenia*, J Clin Psychiatry (2002) 63::1121-1128
24. Niaz, O.S., Haddad, P.M., *Thirty-five months experience of risperidone long-acting injection in a UK psychiatric service including a mirror-image analysis of in-patient care*, Acta Psychiatr Scand (2007) 116::36-46
25. Parellada, E., Adrezina, R., Milanova, V. et al., *Patients in the early phases of schizophrenia and schizoaffective disorders effectively treated with risperidone long-acting injectable*, J Psychopharmacol (2005) 19:(suppl 5)::5-14
26. Moller, J.H., Llorca, P.M., Sacchetti, E., Martin, S.D.D., Medori, R., Parellada, E., *StoRMi Study Group: Efficacy and safety of direct transition to risperidone long-acting injectable inpatients treated with various antipsychotic therapies*, Int Clin Psychopharmacol (2005) 20::121-130
27. Taylor, D.M., Young, CL, Mace, S, Patel, MX., *Early clinical experience with risperidone long-acting injection: a prospective, 6-month follow-up of 100 patients*, J Clin Psychiatry (2004) 65::1076-1083
28. Taylor, D.M., Young, C., Patel, M.X., *Prospective 6-month follow-up of patients prescribed risperidone long-acting injection: factors predicting favourable outcome*, Int J Neuropsychopharmacol (2006) 9::685-694
29. Patel, M.X., Young, C., Samele, C., Taylor, D.M., David, A.S., *Prognostic indicators for early discontinuation of risperidone long-acting injection*, Int Clin Psychopharmacol (2004) 19::233-239
30. Dubois, V.M., Megens, J., Povey, M., Van der Veken, J., *Risperidone long acting in early psychosis: interim results after 6 month follow up*, Program and abstracts of the 161st Annual Meeting of the American Psychiatric Association; May 3-8, 2008; Washington, DC. New research poster NR4-108
31. Thyssen, A., Ning, X., Herben, V. et al., *Pharmacokinetics of long-acting injectable risperidone injected in deltoid muscle compared to gluteal muscle injection in subjects with schizophrenia*, Program and abstracts of the 161st Annual Meeting of the American Psychiatric Association; May 3-8, 2008; Washington, DC. New research poster NR4-003
32. An update on the investigational antipsychotic iloperidone: an expert interview with Andrew J. Cutler, MD. Medscape Psychiatry and Mental Health. April, 2008. Available at: <http://www.medscape.com/viewarticle/571878> Accessed May 25, 2008
33. Weiden, P.J., Di Marino, M., Wolfgang, C.D., *Efficacy of iloperidone in a placebo- and ziprasidone-controlled clinical trial for the treatment of schizophrenia*, Program and abstracts of the 161st Annual Meeting of the American Psychiatric Association; May 3-8, 2008; Washington, DC. New research poster NR4-078
34. Hill, C.L., Phadke, D., Boyce, K.M., *Four-week iloperidone depot injectable: safety and pharmacokinetic profile in patients with schizophrenia and schizoaffective disorder*, Program and abstracts of the 161st Annual Meeting of the American Psychiatric Association; May 3-8, 2008; Washington, DC. New research poster NR4-022
35. Whitehead, C., Moss, S., Cardino, A., Lewis, G., *Antidepressant for people with both schizophrenia and depression*, In: Cochrane Database Syst Rev . Issue 2 CD002305
36. Leucht, S., McGrath, J., White, P., Kissling, W., *Carbamazepine for schizophrenia and schizoaffective psychoses*, In: Cochrane Database Syst Rev . Issue 3 CD001258
37. Casey, D.E., Daniel, D.G., Wassef, A.A., Tracy, K.A., Wozniak, P., Sommerville, K.W., *Effect of divalproex combined with olanzapine or risperidone inpatients with an acute exacerbation of schizophrenia*, Neuropsychopharmacology (2003) 28::182-192
38. Fattinger, K., Roos, M., Vergeres, P. et al., *Epidemiology of drug exposure and adverse drug reactions in two Swiss departments of internal medicine*, Br J Clin Pharmacol (2000) 49::158-167
39. Lieberman, J.A., Stroup, T.S., McEvoy, J.P. et al., *Effectiveness of antipsychotic drugs in patients with chronic schizophrenia*, N E J Med (2005) 353::1209-1223
40. Gopal, S., Steffens, D.C., Kramer, M.L., Olsen, M.K., *Symptomatic remission in patients with bipolar mania: results from a double-blind, placebo-controlled trial of risperidone monotherapy*, J Clin Psychiatry, (2005)
41. Lindenmayer, J.P., Khan, A., *Psychopathology*, In: Lieberman, JA, Stroup, TS, Perkins, DO, eds., *The American Psychiatric Publishing Textbook of Schizophrenia*, Washington, DC, American Psychiatric Publishing; 2006:187-221

42. Trumbetta, S.L., Mueser K.T., *Social functioning and its relationship to cognitive deficits over the course of schizophrenia*, In: Keefe RSE, McEvoy JP, eds. *Negative Symptom and Cognitive Deficit Treatment Response in Schizophrenia*, Washington DC, American Psychiatric Press; 2001:33-67
43. Woo, T.U.W., Zimmet, S.V., Wojcik, J.D., Canuso, C.M., Green, A.I., *Treatment of schizophrenia*, In: Schatzberg, AF, Nemeroff, CB, eds., *The American Psychiatric Publishing Textbook of Psychopharmacology*, 3d ed. Washington DC, American Psychiatric Publishing; 2004:885-912
44. Herz, M.I., Marder, S.R., *Schizophrenia: Comprehensive Treatment and Management*, Philadelphia, Pa: Lippincott Williams & Wilkins; 2002:177-216
45. Swartz, M.S., Perkins, D.O., Stroup, T.S. et al., *Effects of antipsychotic medications on psychosocial functioning in patients with chronic schizophrenia: findings from the NIMH CATIE study*, Am J Psychiatry. 2007;164:428-436
46. Jones, P.B., Barnes, T.R., Davies, L. et al., *Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1)*, Arch Gen Psychiatry, 2006;63:1079-1087
47. Lieberman, J.A., *Is schizophrenia a neurodegenerative disorder? a clinical and pathophysiological perspective*, Biol Psychiatry. 1999;46:729-739
48. Weiden, P., Zygmunt, A., *Medication noncompliance in schizophrenia. Part I. Assessment*, J Pract Psychiatry Behav Health, 1997;3:106-110
49. Davis, J.M., Matalon, L., Watanabe, M.D., Blake, L., Metalon, L., *Depot antipsychotic drugs: place in therapy*, Drugs, 1994;47:741-773