Novel Antipsychotic Use in Schizophrenia

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *summarizes the highlights of a satellite symposium entitled "Treating Schizophrenia: From Clinical Trials to Clinical Practice," held September 23, 1999, at the 12th European College of Neuropsychopharmacology Congress in London, England.*

This symposium was chaired by Robin R. Murray, M.D., F.R.C.Psych, Head of the Department of Psychiatry at the Institute of Psychiatry, and at Guy's, King's, and St. Thomas' Medical Schools, London, England, and cochaired by Nina R. Schooler, Ph.D., Director of Psychiatry Research at Hillside Hospital, Glen Oaks, N.Y. The other participants were Siegfried Kasper, M.D., Professor of Psychiatry and Chairman of the Department of General Psychiatry at the University of Vienna, Austria; Ric M. Procyshyn, M.Sc., Pharm.D., Ph.D., Clinical Psychopharmacologist at the Riverview Hospital, British Columbia, and Clinical Assistant Professor in the Faculty of Pharmaceutical Sciences at the University of British Columbia, Canada; and Zafar A. Sharif, M.D., Assistant Professor of Clinical Psychiatry and Director of the Schizophrenia Research Unit at Columbia University, New York, N.Y.

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Living With Schizophrenia

It is now 100 years since the concept of dementia praecox was first proposed by Kraepelin and then renamed *schizophrenia* by Bleuler. In his later writings, Kraepelin made it clear that he regarded it as a provisional category. Sadly, we are still stuck with this provisional category, said Professor Robin Murray in his presentation. It is often stated that schizophrenia has both positive and negative features. The positive features include the fact that it provides a useful descriptive shorthand among clinicians, it indicates that patients' strange beliefs and actions are due to illness and not willful bad behavior, and it helps to convince the public (sometimes) that psychiatrists know what they are talking about, Professor Murray explained.

Furthermore, it is now clear that the disease concept of dementia praecox/schizophrenia conveys very little of what a true diagnosis should be in etiology and outcome. The term is unreliable in everyday practice; an individual will be regarded as having schizophrenia by one psychiatrist but not by another psychiatrist. There is also no validity to this term—no tests are available to prove a person has schizophrenia. Little is known about the pathogenesis of schizophrenia, and individuals diagnosed with schizophrenia have very different characteristics and outcomes.

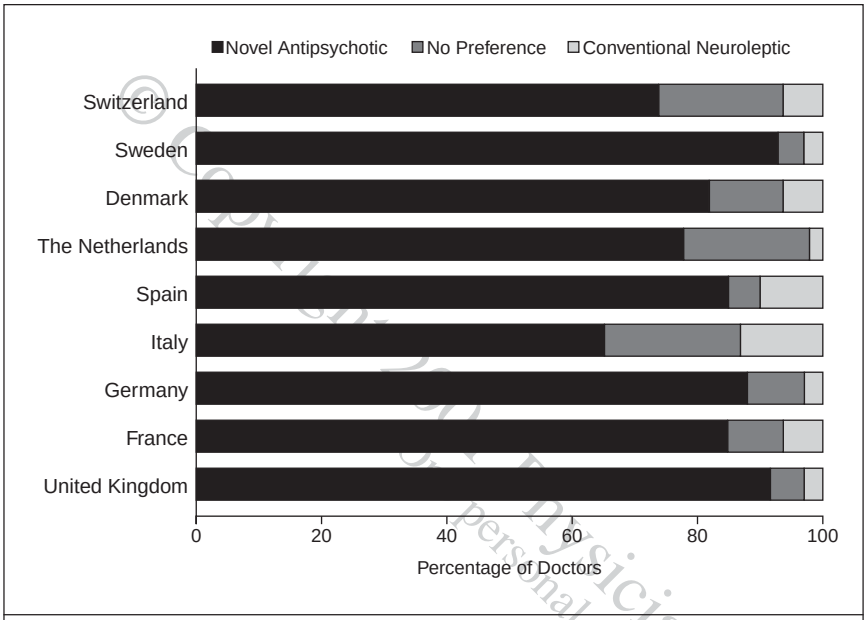
From a patient's perspective, the negative consequences of living with the diagnostic label of schizophrenia is one of the worst aspects of having had psychotic experiences. Many patients dislike the term because it changes the way in which people perceive them. Instead of being regarded as people in their own right, these patients suddenly become part of a group of people classified as being incapable of living a normal life.

Because of these negative aspects of schizophrenia, Professor Murray stated that in his practice, he does not use the term with patients and their relatives unless they themselves make it clear that they find the term useful. He prefers to advise patients that they have a propensity to react to events by having internal experiences that psychiatrists term psychotic, and that both pharmacologic and psychosocial treatments can help to prevent these experiences from recurring.

Professor Murray then addressed the level of care that patients receive across Europe. A recent survey looked at how European psychiatrists (N = 650) thought community care was working in their different countries (Smith-Laittan F, Grundy SB, unpublished data, 1999). Psychiatrists were most content in the Netherlands, where approximately 70% felt care in the community was working satisfactorily. Psychiatrists in Switzerland, Denmark, and Germany were also fairly satisfied, but psychiatrists from Sweden, Spain, Italy, and the United Kingdom felt community care was poor in their countries. These views were closely related to the perceived adequacy of funding in the different countries. Poor quality of care in the community can have a drastic impact on patients through an inability to deliver to them their right to optimum treatment.

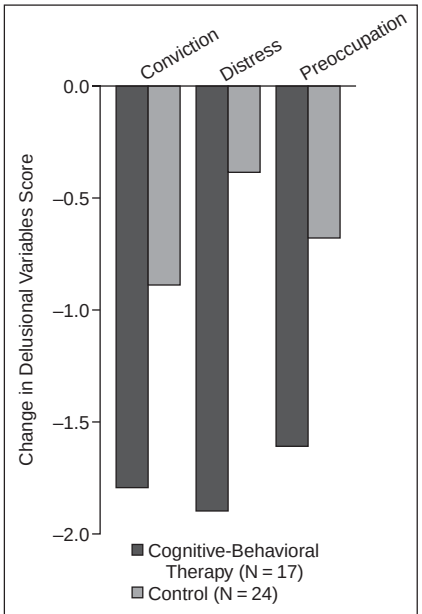
Patients have long complained that the advantages of neuroleptics are often outweighed by their unpleasant side effects, particularly extrapyramidal side effects (EPS), difficulty in thinking, and sexual side effects. Many noncompliant patients do not take their

Figure 1. Psychiatrists' Preference When Prescribing Antipsychotics to a Member of Their Family[a]



[a]Reproduced with permission from Smith-Laittan F and Grundy SB, unpublished data, 1999.

Figure 2. The Effect of Cognitive-Behavioral Therapy on Delusion Variables[a]



[a]Adapted from Kuipers et al.,[2] with permission.

medication because of these side effects. Conventional neuroleptics have a wide range of troublesome side effects and yet patients are expected to continue to take them, Professor Murray stated. He went on to say that, in the United Kingdom at least, when noncompliant patients re-present to their psychiatrist, they will frequently be given a depot conventional neuroleptic with even worse side effects than they experienced with the oral medication. This can lead to the alienation of patients, so, in turn, they become alienated from community services, refuse to comply with treatment, and then deteriorate. Partly as a result of these difficulties, compulsory admissions in England have increased by 50% over the last 5 years.[1] In fact, commented Professor Murray, patients increasingly see the English psychiatric services as imposing social control rather than providing care and support.

He then suggested that the introduction of novel antipsychotics has provided some grounds for optimism for community care of schizophrenia. The survey of 650 European psychiatrists cited above also looked at their views on novel antipsychotics. The results revealed that the majority of psychiatrists, approximately 70% to 90%, would prefer a member of their own family with schizophrenia to receive a novel antipsychotic rather than a conventional neuroleptic (Figure 1). However, only 11% to 15% of psychotic patients are actually receiving novel antipsychotics.

Many patients complain that they rarely have the opportunity to discuss their treatment with their psychiatrist. When they do have such an opportunity, the patients frequently ask for more psychological therapy. Fortunately, there is ample evidence that nonpharmacologic therapies can be highly beneficial for people with schizophrenia. In particular, recent data have emerged that cognitive-behavioral therapy (CBT) can bring benefits. CBT addresses not only the anxiety and depression that accompany psychosis, but can also be directed toward delusions and hallucinations, particularly the former. One recent trial[2] randomly assigned 60 psychotic patients to CBT with standard care or standard care alone. Results revealed that patients receiving CBT had lower overall Brief Psychiatric Rating Scale (BPRS) scores and lower psychosis scores and were less troubled by delusions compared with patients on standard care alone. An analysis of the change in delusional variables (conviction of the truth of their delusion, extent of distress, and preoccupation with delusional beliefs) showed that the rate of improvement was more than double in patients who had CBT (Figure 2).[2] Hence, nonpharmacologic interventions may be valuable adjuncts to drug therapy. Currently, however, a small minority of patients in the United Kingdom actually receive CBT. Combining this with the fact that substantially fewer patients in the United Kingdom receive novel antipsychotics,

which have fewer side effects than conventional neuroleptics, Professor Murray concluded that it appears that only a small proportion of patients are indeed receiving optimal treatment.

Raising Expectations for the Treatment of First-Episode Schizophrenia

Defining first-episode schizophrenia is critical for investigation, stated Dr. Nina Schooler in her presentation. Such identification by clinicians generally occurs at the time that patients are diagnosed, but diagnosis and treatment may occur long after the onset of prodromal signs and even long after the first onset of psychotic symptoms, because this is when patients present at treatment facilities. However, delayed recognition causes delays in starting treatment, which can have serious consequences, such as poorer prognosis and increased costs.

Extensive data have accumulated on the use of conventional neuroleptics in the treatment of schizophrenia. One of the major long-term studies of first-episode schizophrenia was conducted at the Hillside Hospital, New York.[3] Fully 87% of patients in this study showed a robust response to medication, and time to response was 9 weeks. However, response time varied quite considerably, highlighted Dr. Schooler. The likelihood of response was linked to certain patient characteristics such as poor attention and severe hallucinations and delusions at presentation. Also, patients who developed parkinsonism during the treatment period were less likely to respond compared with patients without these signs. More severe symptoms were associated with a history of obstetric complications and being male. The antipsychotic doses for this study were very high, although they were seen as appropriate at the time the study was conducted. Despite this, the response rates were good and hinted at the potential for novel antipsychotics. According to Dr. Schooler, the most important finding from this study was that the cumulative relapse rate over the course of 5 years was as high as 80%. The major predictor of relapse was discontinuation of medication by the patients themselves.

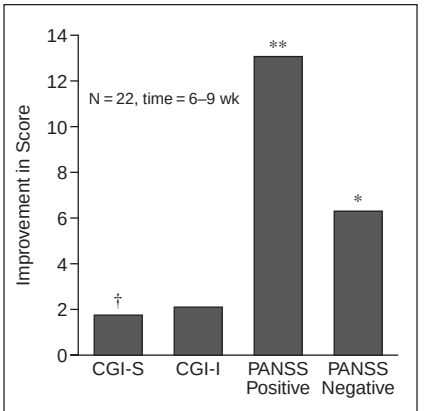
More recently, there have been a number of first-episode studies of novel antipsychotics. One trial[4] investigated the efficacy and tolerability of risperidone in a cohort of untreated patients. These patients improved substantially, mainly in positive symptoms, over the relatively short duration of the trial (6–9 weeks), Dr. Schooler reported (Figure 3).[4] The shorter duration of this trial was perhaps also reflected in the lower response rate (59%) compared with the Hillside Hospital study. The Pittsburgh First-Episode Study[5] looked at 2 cohorts of patients treated with either risperidone or haloperidol. Doses used in the 2 groups were very similar, reaching a maximum of 4.0 mg/day for haloperidol and 4.2 mg/day for risperidone. The courses of response over the year of the study were similar for the 2 cohorts for both positive and negative symptoms. However, a dramatic improvement in positive symptoms was seen within the first 4 weeks, whereas negative symptoms persisted for the duration of the trial, Dr. Schooler explained.

A retrospective analysis of a subgroup of patients from a randomized trial comparing olanzapine with haloperidol was published recently.[6] First-episode schizophrenia was broadly defined as being fewer than 5 years since onset in patients ≤ 45 years old. In this study, improvement in positive symptoms was significantly greater for olanzapine than for haloperidol ($p = .03$), but there was no difference in effect on negative symptoms.

An important issue in these trials is the difference in use of antiparkinsonian medication, said Dr. Schooler. In the Hillside study,[3] a high proportion of patients were taking such medications (90.7%), which is to be expected with the high doses of conventional neuroleptics used. For the comparison of olanzapine and haloperidol, the low dose of olanzapine yielded significantly lower antiparkinsonian medication use than did the low dose of haloperidol ($p = .008$).[6] Dr. Schooler described how in the Pittsburgh study,[5] 94% of patients were taking antiparkinsonian medications concomitantly with haloperidol, even though a low dose was used (4 mg/day), compared with only 37% of risperidone-treated patients ($p = .0003$). The results of that study reflect the tendency toward increased sensitivity to reporting EPS when the dosing schedule is dependent on "neuroleptic threshold" strategies and observation of minimal EPS, noted Dr. Schooler.

Currently, a large randomized trial of low-dose risperidone and haloperidol in early psychosis is underway. The FutuRis study, sponsored by the Janssen Research Foundation, is a

Figure 3. The Effect of Risperidone in a Cohort of Patients With Previously Untreated Schizophrenia[a]



[a]Data from Kopala et al.,[4] Abbreviations: CGI-I = Clinical Global Impressions scale-Improvement, CGI-S = CGI-Severity, PANSS = Positive and Negative Syndrome Scale.
*$p < .01$ vs. baseline.
**$p < .005$ vs. baseline.
†$p < .0002$ vs. baseline.

4-year trial involving approximately 500 patients around the world and is primarily examining long-term outcome. The hypotheses in the study are interesting because, on the basis of previous data, no differences in early response in positive symptoms are expected. However, lower doses, a lower rate of EPS, and reduced use of adjunctive anticholinergic drugs are expected for risperidone compared with haloperidol. In the long term, the expectation is for increased compliance, improved patient satisfaction, better cognitive function, lower relapse rates, and less tardive dyskinesia (TD) with risperidone.

Preliminary baseline data have already been analyzed for this study (data on file, Janssen Research Foundation, 1999). The time interval between first prodromal symptoms and first psychotic episode, 15.9 months, is equal to the duration between first psychotic episode and diagnosis. Mean ages at these points are similar to those seen in previous studies, providing confidence in the data so far. The symptomatology results are also comparable with those of other trials. Of particular interest is that 70% of patients had prior experience with antipsychotic medications. The data revealed that even short exposure to medication affects baseline EPS. However, some patients did experience EPS in the absence of antipsychotic medication, Dr. Schooler highlighted.

Evidence suggests that first-episode patients who come to treatment facilities have been psychotic for a long time, Dr. Schooler concluded. Shortening the duration of unchecked psychosis is an important challenge in schizophrenia. Clinicians must also consider the high sensitivity of first-episode patients to antipsychotic agents and EPS, even at relatively low doses. Novel antipsychotics offer distinct advantages over conventional neuroleptics, so future studies should focus on comparing them with conventional neuroleptics and each other. Dosing strategies for patients in their first episode of schizophrenia should follow the basic guideline of start low and go slow.

Optimal Treatment With Novel Antipsychotics: Choosing the Right Dose

Until quite recently, dosages of up to 100 mg of haloperidol were routinely given to patients with schizophrenia, resulting in high levels of troublesome side effects. The arrival of positron emission tomography (PET) scanning data of the brain indicated that only 5 mg of haloperidol caused dopamine-2 (D_2) receptor occupancy of approximately 80% to 100%, rejecting the need to increase the dose much higher. Correct dosing of antipsychotic drugs should therefore optimize efficacy, tolerability, and, ultimately, patients' long-term outcome, stated Professor Siegfried Kasper in his presentation.

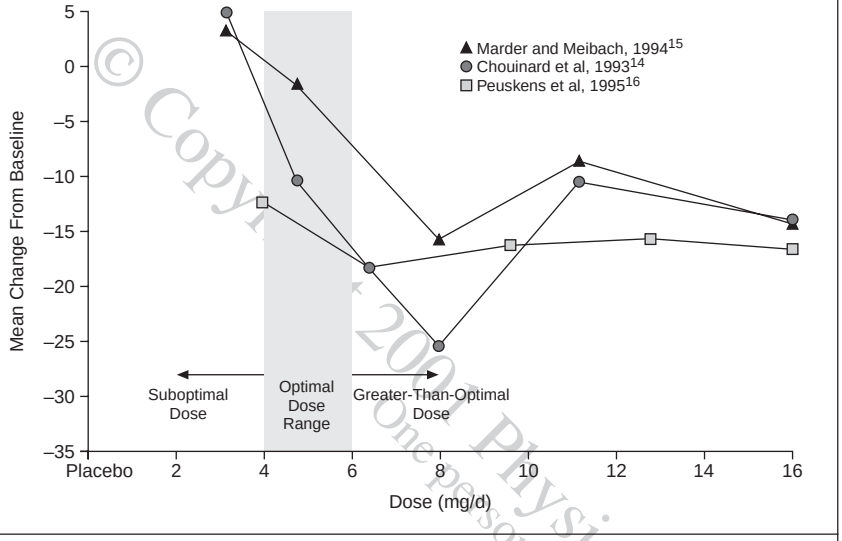
The antipsychotic dose-response relationship demonstrates that antipsychotics plateau at a certain dose, so further increases in dose do not result in greater improvement. It has been suggested that this antipsychotic threshold could correspond to high D_2 receptor occupancy or perhaps that other neurotransmitters are involved. Based on this knowledge, a model of the relationship between plasma drug concentration of conventional neuroleptics and D_2 receptor occupancy rate was developed. It appears that the EPS threshold occurs at 70% to 80% of D_2 receptor occupancy, i.e., doses over this threshold are associated with a significant risk of causing EPS. Plasma drug concentrations are subject to considerable individual variability. For drugs such as clozapine or the phenothiazines, this variation can be 20- or 30-fold. For the newer antipsychotics, the variability is less, perhaps 8- to 10-fold. Because of this variation, no single dosage will be ideal for all patients, so adjustments beyond the "normal" range of doses will be necessary for some patients, Professor Kasper said.

The introduction of conventional neuroleptics was an important breakthrough in the treatment of schizophrenia, but they are associated with a number of limitations. For instance, efficacy is only demonstrated for positive symptoms, not for negative or affective symptoms. Noncompliance, which is frequently related to treatment-emergent side effects, such as EPS, sedation, and disturbances in cognitive function, is a major problem. In contrast, novel antipsychotics have a much broader therapeutic window than the conventional neuroleptics, so doses achieving an antipsychotic effect do not necessarily cause side effects. Nevertheless, Professor Kasper said, it is still necessary to carefully evaluate dosing with these newer drugs to ensure the balance of optimal efficacy with minimal side effects.

The 3 pivotal randomized trials[7] involving risperidone investigated its effects in the dose range of 1 to 16 mg/day. All results demonstrated a clear dose-related response up to 6 mg/day; increasing the dose above this level yielded no benefits in efficacy (Figure 4).[7] These data support the findings of earlier dose-finding studies that the optimal dose of risperidone is 4 to 6 mg/day. The pivotal trials for the novel antipsychotic olanzapine[7] studied the dosages of 5, 10, and 15 mg/day. The results indicate that increasing the dose of olanzapine above 15 mg/day could improve therapeutic response. This view is often shared by clinicians who use olanzapine in real-life settings, said Professor Kasper.

Naturalistic comparisons of risperidone and olanzapine also support the clinical trial data for optimal doses.[8–13] The mean daily dosages used in every-

Figure 4. Change in PANSS Total Score as a Function of Different Daily Doses of Risperidone[a]



[a]Adapted from Kasper,[7] with permission.

Table 1. Comparative Occurrence of Extrapyramidal Side Effects (EPS) During Treatment With Novel Antipsychotics and Conventional Neuroleptics

	EPS Rate (% patients)	
	Comparator	
Drug	Drug	Haloperidol
Risperidone[14–16]	13–16	39
Olanzapine[17]	19	45
Quetiapine[18]	4–8	37
Ziprasidone[19]	0–15	67
Zotepine[20]	5	12

day clinical practice were 2.9 to 5.9 mg/day for risperidone and 12.2 to 17.9 mg/day for olanzapine.

PET data have shown that 4 mg of risperidone corresponds to approximately 75% D_2 occupancy—more evidence to support the optimum dose range of 4 to 6 mg/day. Clinicians are keen to know what doses of the novel antipsychotics result in equivalent potencies, according to Professor Kasper. Evidence so far suggests that 1 mg of risperidone is equipotent to 3 to 4 mg of olanzapine. Therefore, at approximately 75% D_2 receptor occupancy, 4 mg/day of risperidone is equivalent to 10 to 15 mg/day of olanzapine, a reflection of the doses seen in naturalistic studies. Use of such equipotent doses would ensure valid clinical comparisons of these drugs. There are few data for the optimal doses of other novel antipsychotics, but from clinical trials, ≥ 300 mg/day of quetiapine, 160 mg/day of ziprasidone, and 75 to 300 mg/day of zotepine appear to be appropriate. More experience with these drugs is necessary to determine their most effective dosing regimens.

The most important side effects suffered by patients with schizophrenia are EPS. Professor Kasper described the movement disorders characteristic of EPS as stigmatizing and explained that they affect the success of psychotherapeutic rehabilitation programs. Many studies have confirmed that novel antipsychotics are associated with much lower rates of EPS compared with conventional neuroleptics (Table 1).[14–20] For instance, reported EPS rates have been 13% to 16% with risperidone versus 39% with haloperidol,[14–16] 19% with olanzapine versus 45% with haloperidol,[17] and 4% to 8% with quetiapine versus 37% with haloperidol.[18] Furthermore, at doses of up to 8 mg/day of risperidone, the level of EPS is no different from placebo, and risperidone may even reduce preexisting EPS.[7,14,21]

There is also a substantially lower risk of TD with novel antipsychotics compared with conventional neuroleptics such as haloperidol: 0.6% for risperidone versus 2.7%, and 1.6% for olanzapine versus 4.6%. Data on elderly patients with schizophrenia and those with behavioral and psychological symptoms of dementia taking risperidone also demonstrate a low risk for TD.[22–24]

Professor Kasper concluded that the novel antipsychotics have a broader range of efficacy and fewer side effects than conventional neuroleptics, but rational dosing is key to their effective use. Patients should be given an appropriate dose that maximizes efficacy and minimizes side effects.

Using Novel Antipsychotics in Naturalistic Settings

Data from double-blind, randomized clinical trials provide the foundation on which the manufacturers of a drug base their initial dosage guidelines. However, the limited framework and strict entry criteria of these trials make it unlikely that they present a fair picture of clinical reality. This is especially true for schizophrenia, said Dr. Ric Procyshyn in his presentation. Results from naturalistic studies give a more realistic perspective of routine clinical practice and provide real-world data from which clinicians can draw to make treatment decisions and develop clinical guidelines.

Recently, a number of naturalistic studies have been reported. A German retrospective study[25] of patients with

schizophrenia or schizoaffective disorder evaluated the practical use, effectiveness, and side effects of antipsychotics over a period of 4 years. Of the 330 patient records examined, 89 patients were receiving novel antipsychotics; the rest were taking conventional neuroleptics, Dr. Procyshyn reported. The patients on treatment with novel antipsychotics showed improvement in positive and negative symptoms, and they experienced fewer side effects than those treated with conventional neuroleptics. This study also revealed that the more severely ill patients were usually maintained with conventional neuroleptics.

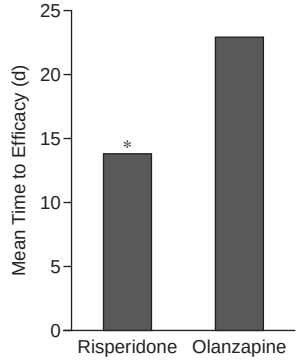
In an open-label prospective, multicenter study[26] of similar patients, subjective experience and well-being during olanzapine treatment were assessed in comparison with unsatisfactory previous medication. Dr. Procyshyn explained that preliminary results at week 14 (the study period was 26 weeks) revealed that olanzapine was superior to previous medication. Significant improvements were seen in overall functioning and well-being. Side effects were significantly less annoying, and olanzapine was preferred by patients over their previous antipsychotic.

Several other naturalistic studies have directly compared the 2 most widely used novel antipsychotics, risperidone and olanzapine. One of the first was conducted at the Riverview Hospital, British Columbia, Canada.[13] The objective of this retrospective study, Dr. Procyshyn commented, was to compare the drug usage patterns, costs, and outcomes of treatment with risperidone (N = 30) and olanzapine (N = 30) in a hospital setting.

The results showed that 60% of risperidone-treated patients were responders compared with only 27% of olanzapine-treated patients ($p < .01$),[13] stated Dr. Procyshyn. Responders were defined as those with a clinically significant reduction in at least one target symptom related to their primary diagnosis and who continued to take their assigned medication. The discharge rate was also significantly different between the groups: 40% for risperidone compared with 13% for olanzapine ($p < .05$). Switching to alternative antipsychotic medication because of side effects or lack of effectiveness occurred in 63% of individuals treated with olanzapine compared with 37% of individuals treated with risperidone ($p < .05$). Furthermore, no differences were found between the groups in occurrence of EPS. Regarding drug usage patterns, it was found that the mean daily dosages for responders were 4.9 mg/day for risperidone and 17.2 mg/day for olanzapine. Translating this into costs for responders (in Canadian dollars) revealed that the cost for one patient taking risperidone was Can $4.69/day compared with Can $11.52/day for olanzapine, Dr. Procyshyn explained.

Currently, a major retrospective naturalistic study called RODOS—the Risperidone and Olanzapine Drug Outcome study in Schizophrenia—is underway.[27] Dr. Procyshyn described the design and objectives as being similar to the Riverview Hospital study and reported that, so far, data are available on 601 patients from 11 sites in 5 countries (the Netherlands, Denmark, Germany, Austria, and Australia), although eventually there will be a database of over 2000 patients. For each center, there are 33 patients per treatment arm, and patients are included if risperidone or olanzapine was the first drug prescribed with the intention of long-term use. The primary measure in this study is the average daily cost of all inpatient drugs, not just the antipsychotics. The secondary measures are average daily dose and cost of studied treatments, discharge rate at 120 days, rates of treatment discontinuation and switching, treatment effectiveness, time to onset of effectiveness, and side effect profiles.

Figure 5. Comparative Time to Onset of Efficacy of Risperidone and Olanzapine in Schizophrenia[a]

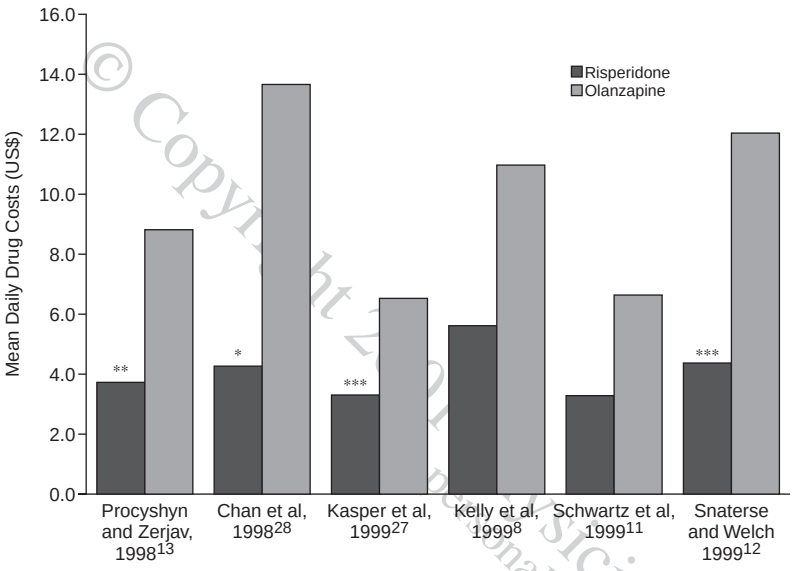


[a]Data from Kasper and Duchesne.[27]
*p = .0008 vs. olanzapine.

This first intent-to-treat (ITT) analysis, over the data collection period of 4 months, indicates that there were no statistically significant differences between olanzapine and risperidone in treatment effectiveness, discharge by 120 days, or treatment discontinuation, Dr. Procyshyn said. Interestingly, however, the onset of action was significantly faster for the risperidone-treated individuals compared with olanzapine-treated patients (14 days vs. 23 days, $p = .0008$; Figure 5).[27] Mean daily doses for responders were 4.8 mg/day for risperidone and 14.3 mg/day for olanzapine. Dr. Procyshyn went on to explain that this means it costs $3.30/day to treat a patient with risperidone successfully compared with $6.50/day to treat an individual with olanzapine.[27]

Looking at these naturalistic studies together, particularly RODOS and the Riverview Hospital study, it appears that the acquisition cost of risperidone is approximately 2 to 4 times lower than that of olanzapine (Figure 6), with no compromise in effectiveness. Furthermore, risperidone appears to be associated with a faster onset of action, fewer cases of treatment discontinua-

Figure 6. Naturalistic Studies Comparing Daily Costs of Treatment With Risperidone and Olanzapine in Schizophrenia



*p < .05 vs. olanzapine.
**p < .001 vs. olanzapine.
***p < .0001 vs. olanzapine.

tion, a higher mean discharge rate, and lower switching rates compared with olanzapine.

With the arrival of novel antipsychotics in the treatment of schizophrenia, interest in the benefits of these drugs has grown to meet increasing demands of patient care. Naturalistic data confirm that it is advantageous to treat individuals with schizophrenia with these drugs rather than conventional neuroleptics. Also, accumulating evidence suggests that risperidone is more cost-effective than olanzapine—an important consideration for clinicians' decision-making processes, concluded Dr. Procyshyn. More studies of this nature will inevitably be conducted in the future, and the findings could have important implications for the treatment of schizophrenia, long-term outcome, and quality of life.

Optimizing Efficacy: The Right Choice

Until we get reliable predictors of response, choosing the best treatment strategy for an individual patient must be based on a careful risk/benefit analysis for that patient, stated Dr. Zafar Sharif in his presentation. Information on efficacy and side effects is obtained primarily from controlled, double-blind clinical trials, while effectiveness data from naturalistic studies provide a much needed dimension on how these drugs perform in the real world. Although results of several large multicenter randomized trials of the efficacy and safety of the novel antipsychotics have been published, it must be emphasized that this is an evolving area of research and any conclusions on relative efficacy of the newer agents are preliminary.

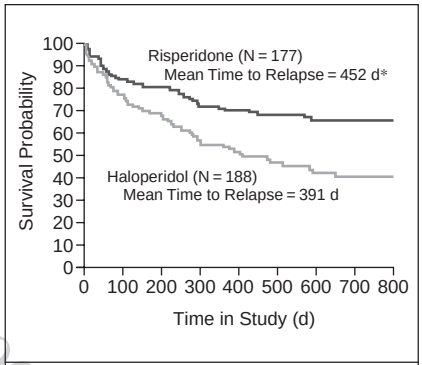
One of the considerations for choice of antipsychotic agent is the type of symptoms exhibited by a patient, said Dr. Sharif. Some of the novel antipsychotics have demonstrated efficacy on a broader range of symptoms compared with conventional agents, including efficacy against negative and depressive symptoms. The largest controlled clinical trial data on the efficacy of risperidone, olanzapine, quetiapine, and ziprasidone compared with conventional neuroleptics come from regulatory trials conducted for marketing approval. Few published studies are available for ziprasidone, but, like quetiapine, it has so far been shown to be equal in efficacy to haloperidol against positive, negative, and affective symptoms in patients with schizophrenia.[18,19,29] Olanzapine, at doses of 10 to 15 mg/day, was superior to haloperidol (10–20 mg/day) against mood symptoms as well as against negative symptoms at 15 mg/day; against psychotic symptoms, it demonstrated equivalent efficacy to haloperidol.[30,31] In the U.S. regulatory trials, risperidone at a dose of 6 mg/day[21] was the only first-line novel antipsychotic that showed superiority to haloperidol (20 mg/day) in all 3 symptom domains (positive, negative, and depressive symptoms). However, in all of these trials, multiple doses of the new agent were compared with a single dose of haloperidol that varied among the different trials. This difference, as well as differences in the patient type that participated in the trials, limits the conclusions we can make on the basis of the regulatory database on relative efficacy profiles of the newer agents, Dr. Sharif explained.

Most of the regulatory database on efficacy is short-term, but preliminary trials of the long-term effectiveness of the newer drugs are also beginning to emerge. Dr. Sharif described a recent double-blind, randomized, multicenter study[22] that investigated relapse prevention with risperidone (N = 177) and

haloperidol (N = 188) in stable outpatients with schizophrenia or schizoaffective disorder over at least 1 year (Figure 7). Mean doses were 4.9 mg/day for risperidone (range, 2–8 mg/day) and 11.7 mg/day for haloperidol (range, 5–20 mg/day); these dose ranges are comparable with doses commonly used in clinical settings. A broad definition of relapse was used to be consistent with clinical practice, including any one or more of the following: rehospitalization, physician judgment that the patient had worsened supported by a 25% increase on Positive and Negative Syndrome Scale (PANSS) score from baseline, significant suicidal/homicidal ideation, deliberate self-injury, or violent/destructive behavior toward others or property.

The analyses demonstrated that the mean time to relapse for risperidone-treated patients was significantly longer than for haloperidol-treated patients (452 days vs. 391 days, p = .001). Similarly, relapse rates for risperidone were significantly lower than for haloperidol: 1-year relapse rates were 23.2% and 34.6% for risperidone and haloperidol, respectively (p = .009). Mean change from baseline on PANSS total, positive symptoms, negative symptoms, disorganized thoughts, and anxiety/depression scores was significantly greater in risperidone-treated patients compared with the haloperidol-treated group. There was no significant difference between the 2 drugs in the treatment of uncontrolled hostility/excitement. Risperidone was also associated with a greater reduction in total Extrapyramidal Symptom Rating Scale score (p = .018) and a lower spontaneously reported rate of TD (0.6% vs. 2.7%) compared with haloperidol. The mean weight gain in risperidone-treated patients was 2.3 ± 0.6 kg, whereas the haloperidol-treated patients demonstrated no significant weight change from baseline. This degree of weight gain with risperidone after 1 year of treatment is similar to that seen in short-term trials lasting 6 to 10 weeks and suggests that most of the weight gain with risperidone occurs in the early phase of treatment and then levels off, highlighted Dr. Sharif.

Figure 7. Time to Relapse in Patients Treated With Risperidone or Haloperidol[a]



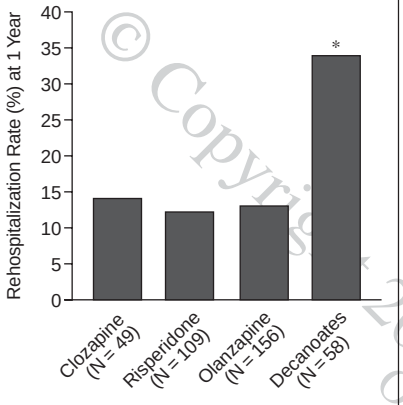
[a]Data from Csernansky et al.[22]
*p = .001 vs. haloperidol.

Another factor that has an impact on the choice of medication is the degree of treatment resistance. Clozapine has consistently been shown to be the drug with the most robust efficacy profile in this unique population. One study[32] of risperidone versus clozapine in patients with treatment-resistant schizophrenia yielded high response rates for both drugs (67% for risperidone and 65% for clozapine) after only 8 weeks of treatment. This study was limited by the inclusion of treatment-intolerant patients who may not have been treatment-refractory and an arbitrary upper-dose limit of 400 mg/day for clozapine. However, 4 other published studies[33–36] and 1 submitted study (Sharif et al., manuscript submitted) all indicate modest efficacy of risperidone in true treatment-refractory patients. In the studies in which response rates were presented, these rates varied between 20% and 25% with risperidone,[35,36] which is clearly superior to the published response rates with conventional neuroleptics (0%–5%)[37,38] but not as high as those reported for clozapine (50%–60%).[39]

Three preliminary studies[38,40,41] of olanzapine in treatment-refractory patients are less consistent. In a rigorous double-blind randomized trial[38] in treatment-refractory patients comparing olanzapine (25 mg/day fixed dose) and chlorpromazine (1200 mg/day fixed dose), olanzapine demonstrated no superiority over chlorpromazine after 8 weeks of treatment. In the second study,[40] which was an open 12-week trial, more patients actually worsened in psychotic symptoms (4 of 16) than improved (2 of 16) when switched from a conventional neuroleptic to olanzapine. The third study,[41] a post hoc analysis of a subgroup of patients from a large international outpatient trial, found that olanzapine was superior to haloperidol in treatment-refractory patients. However, response rates were 45% for olanzapine and 35% for haloperidol; few would consider that this was a truly refractory population with such a high haloperidol-response rate. The results of these studies highlight the importance of how treatment-resistance is defined. In the study by Conley and colleagues,[38] strict Kane criteria were used, whereas in the study by Breier and Hamilton,[41] the criteria for treatment resistance were applied post hoc and were much less strict. This difference in definition of treatment resistance probably accounts for the widely different results.

A few recent studies have evaluated the utility of switching patients from depot antipsychotic maintenance therapy to novel antipsychotics. A multicenter, open study[42] of switching from depot conventional neuroleptics to risperidone in patients desiring a switch revealed that successful switches to risperidone were achieved in 80% of patients after 12 weeks of treatment. There were also significant improvements in PANSS score, less EPS, and less TD compared with depot-medication baseline. Patient sat-

Figure 8. Rehospitalization Rates at 1 Year With Novel Antipsychotics and Depot Conventional Neuroleptics[a]



[a]Data from Conley et al.[44]
*p = .0008 vs. novel antipsychotics.

isfaction was also greater with risperidone. Another open switching study[43] from depot agents to risperidone (N = 12) or olanzapine (N = 12) showed that the majority of patients were successfully switched to either atypical agent for up to 1 year of follow-up, and that both drugs were subjectively well tolerated. In this study, risperidone-treated patients demonstrated statistically significant improvement in symptomatology over 12 months from the depot-medication baseline, whereas the olanzapine-treated group was unchanged in symptom severity from the depot baseline. These preliminary studies suggest that in carefully selected patients (e.g., those with a history of noncompliance secondary to intolerable side effects), switching from a depot neuroleptic to a second generation antipsychotic may be a reasonable option.

Long-term, real-world effectiveness of the novel antipsychotics has been evaluated in a recent naturalistic trial[44] comparing clozapine (N = 49), risperidone (N = 109), and olanzapine (N = 156) with depot conventional neuroleptics (N = 58). The readmission rates for patients taking any of the novel antipsychotics were very low—between 12% and 14%—compared with 34% for patients taking depot medication (Figure 8). Mean time to relapse was not significantly different between the various treatment groups and was approximately 150 days for clozapine, olanzapine, and the depot agents and 250 days for risperidone. Whether the lower relapse rates with the newer drugs are related to improved compliance, superior efficacy, or are just a spurious finding related to baseline differences in study group populations remains to be determined.

Conclusion

As we gain more experience with novel antipsychotics, the relative advantages and disadvantages of these drugs will become clearer in terms of their range of efficacy, differing side effect profiles, and cost. Naturalistic studies and valid head-to-head comparisons, using equipotent doses, will help formulate rational decision-making guidelines. Ultimately, the aim is to optimize the treatment of patients with schizophrenia to maximize their functioning and improve their quality of life and long-term outcome.

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