Clinical effectiveness in first-episode patients

Ruth I. Ohlsen[a,*], Mary S. O'Toole[a], Rick G. Purvis[a], James T.R. Walters[b],
Teresa M. Taylor[b], Hugh M. Jones[b], Lyn S. Pilowsky[a]

[a]*Section of Neurochemical Imaging, Institute of Psychiatry, De Crespigny Park, Box 54, London, SE5 8AF, UK*
[b]*South London and Maudsley NHS Trust, Maudsley Hospital, Denmark Hill, London, UK*

Abstract

Managing patients with first-episode schizophrenia is a challenging task for psychiatrists. Early diagnosis and effective intervention are vital to achieving long-term positive clinical outcomes among first-episode patients. Although these patients are the most responsive to treatment, they are also more susceptible to adverse events. The efficacy and improved tolerability associated with the newer atypical antipsychotics means that these drugs can be used successfully in the treatment and long-term management of schizophrenia from the onset of illness. However, as well as managing the symptoms of the disease, pharmacological treatments need to meet the broader requirements of clinical effectiveness that encompass all of the outcome domains associated with schizophrenia. This article will discuss available data on atypical antipsychotics in first-episode patients and present the primary results from the FIRST (Southwark first-onset psychosis) study, which examined the use of quetiapine for the first-line management of schizophrenia as part of a specialist episode psychosis service.
© 2004 Elsevier B.V. and ECNP. All rights reserved.

Keywords: First episode; Schizophrenia; Clinical effectiveness; Antipsychotic; FIRST; Quetiapine

1. Introduction

Schizophrenia is a chronic, debilitating disorder and is regarded as the most devastating of all the mental illnesses. It is associated with significant functional impairment and patient mortality, with approximately 10% of patients with schizophrenia committing suicide (Caldwell and Gottesman, 1992). The clinical presentation, course and severity of schizophrenia are complex and this impacts significantly on the effective treatment and long-term management of patients. Early intervention at the onset of illness has been shown to be an important prognostic factor for the subsequent course of schizophrenia (Linszen et al., 1998; Linszen and Dingemans, 2002; McGlashan, 2001; Woods and McGlashan, 2002).

For first-episode patients, as with all patients diagnosed with schizophrenia, successful long-term management relies upon treatment that encompasses the six schizophrenia outcome domains: symptoms of disease, tolerability, every-day functioning, subjective well-being, family/carer burden and treatment adherence, which collectively contribute to the broader concept of clinical effectiveness. Although first-episode patients are generally the most responsive to pharmacological treatment, they frequently have difficulty accepting their diagnosis and fail to engage with their therapy, leading to treatment delay. Early intervention with assertive and effective therapy can potentially enhance the therapeutic alliance, reduce the risk of patient relapse and improve long-term morbidity (DeQuardo, 1998). In some studies, delays in initial treatment have been found to be associated with cognitive impairment, a decreased likelihood of returning to premorbid function and a less successful clinical outcome (Loebel et al., 1992).

The patient's initial experience of treatment also has a significant impact on long-term outcome and adherence.

* Corresponding author. Tel.: +44 207 848 5117; fax: +44 207 848 0837.
E-mail address: r.ohlsen@iop.kcl.ac.uk (R.I. Ohlsen).
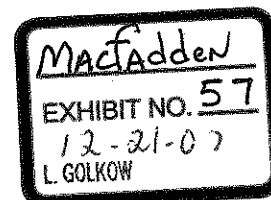
First-episode patients are twice as likely to be initially medicated against their will. Supporters of early intervention believe the first episode constitutes a 'critical therapeutic window' for successful care (Birchwood et al., 1998), preventing further potentially traumatic and irreparable damage to psychological, vocational and social support networks.

Even if these patients engage with their treatment regimen and agree to take prescribed medication, many first-episode patients become non-adherent to conventional antipsychotic regimens. Up to one-third of patients may not respond to treatment with conventional antipsychotics (Brenner et al., 1990) which cause many side effects, particularly extrapyramidal symptoms (EPS) such as parkinsonism, dystonia, akathisia and tardive dyskinesia (Levinson et al., 1990). In addition, among first-episode patients the incidence of relapse is high, with >80% of individuals relapsing within 5 years after initial recovery (Robinson et al., 1999). Non-adherence to medication is an important factor in this high rate of relapse.

2. Clinical effectiveness of atypical antipsychotics in first-episode patients

It has been suggested that newer atypical antipsychotic drugs are efficacious and better tolerated treatments for first-episode psychosis than conventional agents. Recent guidelines published in the UK advocate the use of atypical antipsychotic treatment in first-episode psychosis and provide specific guidance advising the continuation of antipsychotic drug therapy for up to 2 years following the onset of psychosis (NICE, 2002). However, there has been limited investigation into the clinical effectiveness of these drugs encompassing the six outcome domains in first-episode patients with schizophrenia. Several studies have highlighted the efficacy and tolerability of atypical antipsychotics (risperidone, olanzapine and quetiapine) in first-episode patients, although these have been primarily over a short-time period (Bobes et al., 2003; Emsley and on behalf of the Risperidone Working Group, 1999; Good et al., 2002; Kopala et al., 1998; Merlo et al., 2002; Montes et al., 2003; Sanger et al., 1999; Tauscher-Wisniewski et al., 2002). Unfortunately, long-term data are lacking on the use of atypical antipsychotic drugs in first-episode, newly treated psychotic patients, although a number of long-term studies are ongoing (Keefe et al., 2004; Lieberman et al., 2003).

2.1. Risperidone

A short-term study by Kopala et al. (1997) assessing the effectiveness of risperidone in 22 patients with first-episode psychosis showed that both low (2–4 mg) and high (5–8 mg) doses of risperidone were efficacious among this patient population. However, patients receiving low-dose

risperidone showed significantly greater improvements in Positive and Negative Syndrome Scale (PANSS) positive, negative, general symptoms and total score, compared with patients in the high-dose risperidone group (Kopala et al., 1997). Lane et al. (2001), in a double-blind, fixed-dose, 6-week study comparing the efficacy of low-dose (3 mg/day) and high-dose (6 mg/day) risperidone in first-episode patients ($n=24$), reported favourable efficacy for both low and high doses of risperidone, although the high-dose group tended to display reduced tolerability to risperidone. In addition to improved PANSS scores, first-episode patients have also shown improvements in overall functioning and depressive symptoms, as measured by Global Assessment of Functioning (GAF) and Clinical Global Impression (CGI) scales, following treatment with risperidone monotherapy (Kopala et al., 1998; Yap et al., 2001). In terms of tolerability, lower doses of risperidone induced fewer EPS in first-episode patients (Emsley and on behalf of the Risperidone Working Group, 1999; Kopala et al., 1997; Lane et al., 2001), compared with patients who were treated with a high dose of risperidone, 32% of whom developed mild akathisia and parkinsonism (Kopala et al., 1997).

When compared with conventional antipsychotics such as haloperidol, risperidone has been shown to display better efficacy in patients with first-episode psychosis (Emsley and on behalf of the Risperidone Working Group, 1999). At endpoint in this double-blind study ($n=183$), 63% of risperidone-treated patients displayed clinical improvement compared with 56% of haloperidol-treated patients (Emsley and on behalf of the Risperidone Working Group, 1999). Risperidone was also better tolerated than haloperidol in patients, with the severity of EPS and the requirement for antiparkinsonian medication significantly lower in the risperidone group (Emsley and on behalf of the Risperidone Working Group, 1999). Long-term studies comparing the efficacy of risperidone with conventional agents have shown similar efficacy; however, a lower number of patient hospitalisations, shorter hospitalisation times, sustained symptomatic improvements and fewer drug-induced EPS have been reported in patients receiving risperidone (Gutierrez et al., 2002; Malla et al., 2001; Merlo et al., 2002).

2.2. Olanzapine

To date, four studies have evaluated the efficacy and safety of olanzapine in first-episode patients with schizophrenia (Bobes et al., 2003; Lieberman et al., 2003; Montes et al., 2003; Sanger et al., 1999). Sanger et al. (1999) examined a subgroup of first-episode patients ($n=83$) from a large prospective, multicentre, international study comparing olanzapine and haloperidol. A significantly higher clinical response (>40% reduction in Brief Psychiatric Rating Scale [BPRS] total score) was reported for the olanzapine-treated patients (67.2%) than for the haloperidol

group (29.2%). In addition, significantly fewer EPS were reported in the olanzapine group (Sanger et al., 1999). Similarly, in a recent study of first-episode patients (n=158) from a large prospective open trial of patients with schizophrenia, treatment with olanzapine showed a significantly higher clinical response, with significant lowering of total BPRS and CGI scores compared with conventional antipsychotic therapy. Fewer EPS were also reported with olanzapine compared with conventional antipsychotics (Bobes et al., 2003).

In an observational, naturalistic 24-week study (n=182), olanzapine produced similar improvements to risperidone and conventional antipsychotics on CGI Severity of Illness and GAF scales, although olanzapine and risperidone displayed greater quality of life improvements compared with conventional antipsychotics (Montes et al., 2003). EPS symptoms were also significantly lower in the olanzapine-treated patients than in the risperidone and conventional antipsychotic treatment groups (Montes et al., 2003). Lieberman et al. (2003), reporting the results from the 12-week acute phase of a long-term (2-year), randomised, double-blind trial, demonstrated a therapeutic advantage for olanzapine over haloperidol in first-episode patients (n=263), in terms of symptom reduction and treatment retention. Although olanzapine exhibited a lower incidence of EPS in this study, it was associated with greater weight gain (7.8 kg vs. 2.6 kg) (Lieberman et al., 2003).

2.3. Quetiapine

Quetiapine has demonstrated efficacy in acutely relapsed psychotic patients (Arvanitis and Miller, 1997; Borison et al., 1996; Fabre Jr. et al., 1995; King et al., 1998), with a low propensity to induce EPS and tardive dyskinesia. In a recent short-term study of patients (n=14) experiencing a first-episode of schizophrenia, statistically and clinically significant reductions in psychopathology were observed in 71% of patients following treatment with quetiapine (Tauscher-Wisniewski et al., 2002). Improvements in PANSS subscales and significant improvements in cognitive performance have also been reported in an interim analysis of a 2-year, open-label study in young patients (n=34) with first-episode psychosis treated with quetiapine (mean dose 517.9 mg/day) (Good et al., 2002).

The Southwark first-onset psychosis study (FIRST) was designed to provide a detailed audit of the use of quetiapine for first-line management of schizophrenia as part of a specialist first-episode service (outpatient mental health team based in the London Borough of Southwark), and to evaluate clinical effectiveness in a "real-world" setting by assessing most of the outcome domains of clinical effectiveness (disease symptoms, tolerability, functioning/well-being), which encompass everyday functioning and subjective well-being, and treatment adherence.

A total of 33 patients (aged ≥16 years) who had experienced a first episode of psychosis or had been out of contact with services for >6 months with an active illness of <2 years were recruited into the study (22 men, 11 women). The mean age was 29.2 (SD 9.8) years; 54.5% of patients were from ethnic minority groups. Sixty-four percent (n=21) of patients met ICD-10 diagnostic criteria for schizophrenia, 9% (n=3) for delusional disorders and 27% (n=9) for schizoaffective disorder (WHO, 1992). At 1 year, patient discontinuations were attributable to patient dropout (n=4), discharge from service (n=11) and transfer to other services (n=3). Quetiapine was the first-line drug for all participants in the study, and for 66% of patients (n=22) quetiapine was their first exposure to antipsychotic medication. Thirty-three percent of patients (n=11) had experienced brief exposure to other antipsychotics prior to the study, but were switched to quetiapine due to intolerable side effects (hyperprolactinaemia, akathisia) or lack of clinical response. Patients were prescribed quetiapine starter packs, which gradually increased the dose of quetiapine from 50 to 300 mg/day over a period of 4–8 days. Doses were then titrated according to clinical response and tolerability by the treating physicians. The mean dose of quetiapine was 360.4 (SD 148.9) mg/day at week 6 and 431.8 (SD 176.4) mg/day at week 48.

Analysis of quetiapine efficacy in patients showed statistically and clinically significant symptomatic and functional improvements over time on each of three clinical rating scales (PANSS, BPRS and Calgary Depression Scale for Schizophrenia [CDSS]). Treatment with quetiapine resulted in a significant reduction in PANSS total, positive, negative and general psychopathology scores throughout the study (all $P<0.001$ vs. baseline at weeks 6, 12, 24, 36 and 48) (Fig. 1). There was also a significant improvement in depressive symptoms after 6 weeks of treatment ($P<0.05$ vs. baseline) (Fig. 2) which was maintained over 1 year.

EPS were rated at each time point using the Simpson-Angus Scale (SAS), Barnes Akathisia Scale (BAS) and
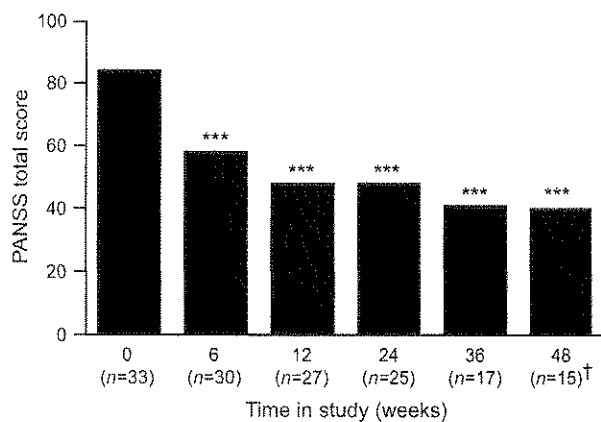
***$P<0.001$ vs baseline
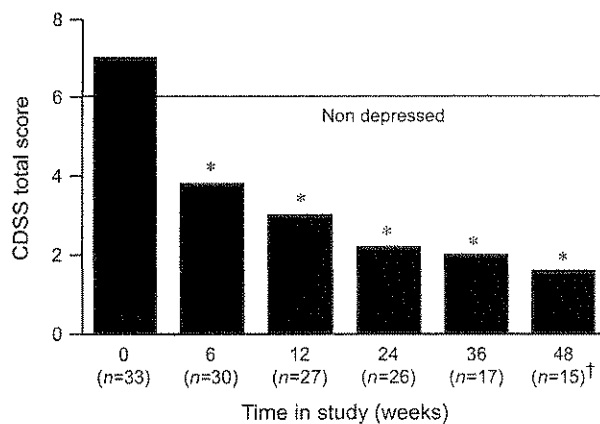[†]Numbers do not reflect drop-out rates

Fig. 1. Mean change in PANSS total score from baseline to weeks 6, 12, 24, 36 and 48.

Abnormal Involuntary Movement Scale (AIMS). There were negligible treatment-emergent EPS and no cases of tardive dyskinesia were seen. Although somnolence was not systematically evaluated in the study, most patients reported a degree of somnolence during the initial stages of quetiapine therapy. However, this was transient and most patients felt less sedated after approximately 3 weeks of treatment. No evidence of clinical hyperprolactinaemia was noted and there were no reports of sexual side effects or amenorrhoea.

In the present study, a statistically significant improvement in overall functioning, as measured by the GAF scale, was observed after 6 weeks and continued throughout 1 year of treatment (Fig. 3). Scores on the Schizophrenia Quality of Life Scale (SQLS), measuring subjective quality of life, indicated a statistically significant improvement in psychological well-being over 1 year of follow up. Scores on the symptoms/side-effect subscale were consistently low at baseline but still indicated an improvement over 1 year of treatment. Similarly, scores on the Drug Attitude Inventory (DAI-10) showed that there appeared to be a general trend towards improvement after 1 year of treatment intervention, suggesting a positive attitude.

As the study progressed, an increasing number of patients were treated on an outpatient basis. Employing a mirror-image approach, a retrospective comparison between the treatment approach used during the study and a standard treatment approach used in an age- and sex-matched sample was analysed. Reduced patient readmission and higher engagement rates were observed in the F1RST patients compared with the matched patient group.
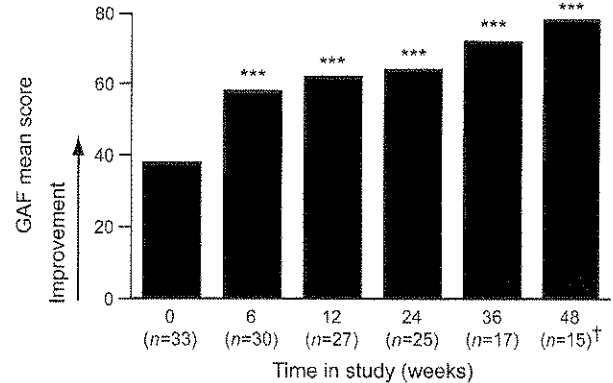
These findings support the use of quetiapine in the early treatment of first-episode psychosis and reflect previous research evidence (Tauscher-Wisniewski et al., 2002). Given the lack of research in this area, these findings will undoubtedly contribute to the evidence base for the use of

***$P<0.001$ vs baseline
†Numbers do not reflect drop-out rates

Fig. 3. Mean improvement in global functioning from baseline to weeks 6, 12, 24, 36 and 48.

better tolerated atypical antipsychotic drugs in the modern management of patients with first-episode psychosis.

3. Maximising clinical effectiveness in first-episode patients

3.1. Improved tolerability

There are important differences between antipsychotic medications, and careful selection of an appropriate agent with a good tolerability profile will ensure that minimal problems will arise for both patients and their carers. As described earlier, recent studies have highlighted the improved tolerability profile of atypical antipsychotics compared with conventional antipsychotics, particularly the reduced incidence of EPS in first-episode patients. However, there are differences in tolerability between atypical antipsychotics, such as risperidone when used at high doses (Kopala et al., 1997). One of the most distressing adverse events associated with antipsychotic medication is weight gain, particularly for women. Preventing weight gain in first-episode patients may have significant short- and long-term benefits in terms of minimising morbidity, mortality and the economic impact of obesity (Fontaine et al., 2001). This is important as previous research has shown that standard psychosocial intervention has little impact in patients who are already obese (Ohlsen et al., 2003). Weight gain has been reported in first-episode patients treated with risperidone (Gutierrez et al., 2002; Merlo et al., 2002) and olanzapine (Lieberman et al., 2003; Montes et al., 2003; Sanger et al., 1999). In the 6-week study by Sanger et al. (1999), a significant mean weight increase of 4.1 kg ($P<0.001$) was recorded for patients treated with olanzapine compared with a mean weight increase of 0.5 kg for haloperidol-treated individuals. Similarly, Lieberman et al. (2003) reported a mean weight increase of more than 7.0 kg in first-episode patients treated with olanzapine compared

*$P<0.05$ vs baseline
†Numbers do not reflect drop-out rates

Fig. 2. Mean change in CDSS total score from baseline to weeks 6, 12, 24, 36 and 48.

with a 2.6 kg increase for haloperidol-treated patients (*P*<0.001) during the 12-week acute phase of a long-term study. In the olanzapine group, 61.5% of the patients had a >7% increase in their body weight from baseline, compared with 22.7% of haloperidol-treated patients (*P*<0.001) (Lieberman et al., 2003). Other non-EPS effects, which patients can find distressing, have also been reported following treatment with conventional and atypical antipsychotics. Increased prolactin levels were significantly greater in patients with first-episode psychosis treated with haloperidol compared with those treated with olanzapine (Sanger et al., 1999). Diminished sexual desire and amenorrhoea have also been reported in first-episode patients following treatment with risperidone (Gutierrez et al., 2002; Merlo et al., 2002).

Patients and their carers must be informed of any potential side effects associated with the prescribed medication as this can improve treatment adherence. However, tolerability is only one factor affecting adherence to medication. Other factors, such as poor insight into the disease, need further investigation in this patient group.

3.2. Dosing

In order to ensure an atypical agent is clinically effective, it is important that dosing is adequate. There is a perception that with some atypical antipsychotics the dose used in first-episode patients should be lower than that used in patients with chronic schizophrenia (Emsley and on behalf of the Risperidone Working Group, 1999). In the FIRST study, few tolerability problems associated with the initiation of quetiapine treatment were seen; transient sedation was the only adverse event observed. However, studies examining the efficacy of risperidone in first-episode patients highlighted increased tolerability problems particularly in relation to EPS, that were associated with higher doses of this agent (Emsley and on behalf of the Risperidone Working Group, 1999; Kopala et al., 1997). Quetiapine was initiated up to 300 mg/day within the first week of the FIRST study and the dose was increased over the first 4–6 weeks. Results from this study indicate that the lower dosage requirements observed previously in this patient group may be drug specific. Therefore, drugs that cause dose-dependent EPS, such as risperidone and olanzapine, may be more problematic in first-episode patients and should be investigated further.

3.3. Improving adherence to medication

3.3.1. Treatment adherence
Many first-episode patients hold the view that they have already been treated and therefore do not require further treatment, and that they would not become ill again. Continued treatment adherence is crucial for achieving improved patient outcomes in first-episode patients, particularly when approximately 40% of patients with schizo-

phrenia fail to adhere to their prescribed medication (MacEwan, 1993). Currently, few data are available on adherence rates in first-episode patients treated with atypical antipsychotics; however, a recent study reported that almost 60% of patients (*n*=186) were non-adherent or inadequately adherent after 1 year (Coldham et al., 2002). Despite non-adherence to medication, there is clear evidence for an enhanced treatment alliance as more than 80% of patients were still engaged with the service and were willing to return as soon as 'warning signs', determined collaboratively with patients, appeared. Lieberman et al. (2003) have reported that significantly more patients treated with olanzapine remained in their study compared with patients treated with haloperidol. The authors suggested that as atypical drugs are associated with better long-term adherence, there is a potentially lower risk of symptomatic recurrence, as occurs in patients with chronic disorders.

Developing a therapeutic alliance is integral to promoting adherence and identifying and understanding patient needs and treatment expectations. An equally important component of this alliance is improving the patient's own understanding and acceptance of their illness and the need for adherence to treatment.

3.3.2. Positive attitude to treatment
In a retrospective study by Malla et al. (2001), significant improvements in terms of reduced length of hospitalisation, total number of days spent in hospital subsequent to first admission, number of admissions per year and days spent in the hospital as a proportion of total time in treatment were seen in first-episode patients treated with risperidone compared with patients receiving conventional antipsychotics. In the FIRST study, patients recruited into the FIRST study strongly identified with the study team's approach, goals and philosophies. Interestingly, patients continually emphasised the team's unique and positive approach compared with other treatments of which they were aware. This is reflected by the higher rate of engagement and reduced patient readmission observed compared with similar patients receiving standard treatment.

3.3.3. Family attitudes
Family attitudes can have a significant impact in first-episode patients. Some family members will be devastated by the diagnosis, while others may underestimate the illness severity and requirement for long-term treatment. Although gaining the family or carer view of patient progress would be beneficial, the practicalities of getting carers and family members to fill in rating scales are often difficult and frequently impossible. It is important to educate both the patient and carer about the disease, treatment regimen, tolerability issues and potential signs of relapse. Clear and effective communication between all parties plays a vital role in improving and maintaining treatment adherence.

3.3.4. Continuity of care

The organisation of psychiatric services is also essential for delivering clinically effective treatment in first-episode patients. Continuity of care is important and problems may occur when patients are transferred from an inpatient to an outpatient setting. In addition, more emphasis should be put on successfully reintegrating first-episode patients into their workplace or school and into the wider community. Usually only 15–30% of patients achieve this vocational reintegration so, from an employment perspective, treatment programmes that do not include a specific focus for retraining continue to be less successful (Dickson et al., 2001; Turgay et al., 2002). Including a job coach in the therapeutic alliance may represent one solution to this issue.

4. Conclusions

It is now accepted that patients with schizophrenia and other related psychotic disorders are more responsive to treatment in the early stages of illness. Consequently, the treatment of patients experiencing their first psychotic episode is of critical importance. The longer patients experience symptoms, the more likely that they are to develop persistent cognitive and functional impairment. Although first-episode patients are the most responsive to treatment, they are also the most susceptible to adverse events.

Clinical evidence to date suggests that the atypical antipsychotics (quetiapine, olanzapine and risperidone) are effective treatments in first-episode schizophrenia, with statistically and clinically significant symptomatic and functional improvement being sustained throughout treatment. Improvements are also seen in patients' quality of life, with a reduced or negligible incidence of side effects. Further long-term comparative studies in first-episode patients are needed. However, as well as managing the symptoms of disease, pharmacological treatments need to meet the broader requirements of clinical effectiveness that encompass all of the outcome domains associated with schizophrenia. Rather than giving such prominence to the symptoms traditionally assessed in clinical trials, subjective measures of improvement in first-episode patients should be compared across the different atypical antipsychotics. Whether patients actually want to take their medication should also be considered. Evidence from dedicated early intervention services, such as the FIRST study using quetiapine, support the notion that by addressing issues such as adherence and providing flexibility in contacts with patients and carers, high engagement rates and low hospitalisation rates can be successfully achieved.

Overall, the important issues for achieving clinical effectiveness in first-episode psychosis are a positive treatment experience resulting in maintenance of recovery and relapse prevention, good tolerability, education of the family, continuity of care and reintegration.

References

Arvanitis, L.A., Miller, B.G., the Seroquel Trial 13 study group, 1997. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. Biol. Psychiatry 42, 233–246.

Birchwood, M., Todd, P., Jackson, C., 1998. Early intervention in psychosis. The critical period hypothesis. Br. J. Psychiatr., Suppl. 172, 53–59.

Bobes, J., Gibert, J., Ciudad, A., Alvarez, E., Canas, F., Carrasco, J.L., Gascon, J., Gomez, J.C., Gutierrez, M., 2003. Safety and effectiveness of olanzapine versus conventional antipsychotics in the acute treatment of first-episode schizophrenic inpatients. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 27, 473–481.

Borison, R.L., Arvanitis, L.A., Miller, B.G., US Seroquel Study Group, 1996. ICI 204,636, an atypical antipsychotic: efficacy and safety in a multicenter, placebo-controlled trial in patients with schizophrenia. J. Clin. Psychopharmacol. 16, 158–169.

Brenner, H.D., Dencker, S.J., Goldstein, M.J., Hubbard, J.W., Keegan, D.L., Kruger, G., Kulhanek, F., Liberman, R.P., Malm, U., Midha, K.K., 1990. Defining treatment refractoriness in schizophrenia. Schizophr. Bull. 16, 551–561.

Caldwell, C.B., Gottesman, I.I., 1992. Schizophrenia—a high-risk factor for suicide: clues to risk reduction. Suicide Life-Threat. Behav. 22, 479–493.

Coldham, E.L., Addington, J., Addington, D., 2002. Medication adherence of individuals with a first episode of psychosis. Acta Psychiatr. Scand. 106, 286–290.

DeQuardo, J.R., 1998. Pharmacologic treatment of first-episode schizophrenia: early intervention is key to outcome. J. Clin. Psychiatry 59 (Suppl. 19), 9–17.

Dickson, R.A., Glazer, W.M., Violato, C., 2001. A computerized self-report questionnaire for assessing sexual functioning in psychotic patients: the DGSF scale. Schizophr. Res. 49 (Suppl. 1), 283.

Emsley, R.A., on behalf of the Risperidone Working Group, 1999. Risperidone in the treatment of first-episode psychotic patients: a double-blind multicenter study. Schizophr. Bull. 25, 721–729.

Fabre Jr., L.F., Arvanitis, L., Pultz, J., Jones, V.M., Malick, J.B., Slotnick, V.B., 1995. ICI 204,636, a novel, atypical antipsychotic: early indication of safety and efficacy in patients with chronic and subchronic schizophrenia. Clin. Ther. 17, 366–378.

Fontaine, K.R., Heo, M., Harrigan, E.P., Shear, C.L., Lakshminarayanan, M., Casey, D.E., Allison, D.B., 2001. Estimating the consequences of anti-psychotic induced weight gain on health and mortality rate. Psychiatry Res. 101, 277–288.

Good, K.P., Kiss, I., Buiteman, C., Woodley, H., Rui, Q., Whitehorn, D., Kopala, L., 2002. Improvement in cognitive functioning in patients with first-episode psychosis during treatment with quetiapine: an interim analysis. Br. J. Psychiatry 43, s45–s49.

Gutierrez, F.M., Segarra, E.R., Gonzalez-Pinto, A.A., Martinez, J.G., 2002. Risperidone in the early treatment of first-episode psychosis: a two-year follow-up study. Actas Esp. Psiquiatr. 30, 142–152.

Keefe, R.S., Seidman, L.J., Christensen, B.K., Hamer, R.M., Sharma, T., Sitskoorn, M.M., Lewine, R.R., Yurgelun-Todd, D.A., Gur, R.C., Tohen, M., Tollefson, G.D., Sanger, T.M., Lieberman, J.A., 2004. Comparative effect of atypical and conventional antipsychotic drugs on neurocognition in first-episode psychosis: a randomized, double-blind trial of olanzapine versus low doses of haloperidol. Am. J. Psychiatry 161, 985–995.

King, D.J., Link, C.G.G., Kowalcyk, B., 1998. A comparison of bd and tid dose regimens of quetiapine (Seroquel) in the treatment of schizophrenia. Psychopharmacology (Berl.) 137, 139–146.

Kopala, L.C., Good, K.P., Fredrikson, D., Whitehorn, D., Lazier, L., Honer, W.G., 1998. Risperidone in first-episode schizophrenia: improvement in symptoms and pre-existing extrapyramidal signs. Int. J. Psychiatry Clin. Pract. 2, S19–S25.

Kopala, L.C., Good, K.P., Honer, W.G., 1997. Extrapyramidal signs and clinical symptoms in first-episode schizophrenia: response to low-dose risperidone. J. Clin. Psychopharmacol. 17, 308–313.

Lane, H.Y., Chang, W.H., Chiu, C.C., Huang, M.C., Lee, S.H., Chen, J.Y., 2001. A pilot double-blind, dose-comparison study of risperidone in drug-naive, first-episode schizophrenia. J. Clin. Psychiatry 62, 994–995.

Levinson, D.F., Simpson, G.M., Singh, H., Yadalam, K., Jain, A., Stephanos, M.J., Silver, P., 1990. Fluphenazine dose, clinical response, and extrapyramidal symptoms during acute treatment. Arch. Gen. Psychiatry 47, 761–768.

Lieberman, J.A., Tollefson, G., Tohen, M., Green, A.I., Gur, R.E., Kahn, R., McEvoy, J., Perkins, D., Sharma, T., Zipursky, R., Wei, H., Hamer, R.M., HGDH Study Group, 2003. Comparative efficacy and safety of atypical and conventional antipsychotic drugs in first-episode psychosis: a randomized, double-blind trial of olanzapine versus haloperidol. Am. J. Psychiatry 160, 1396–1404.

Linszen, D., Dingemans, P.M., 2002. Is early intervention effective? Schizophr. Res. 53 (Suppl. 14).

Linszen, D., Lenior, M., De Hann, L., Dingemans, P.M., Gersons, B., 1998. Early intervention, untreated psychosis and the course of early schizophrenia. Br. J. Psychiatr., Suppl. 172, 84–89.

Loebel, A.D., Lieberman, J.A., Alvir, J.M.J., Mayerhoff, D.I., Geisler, S.H., Szymanski, S.R., 1992. Duration of psychosis and outcome in first-episode schizophrenia. Am. J. Psychiatry 149, 1183–1188.

MacEwan, G.W., 1993. New antipsychotic medications: do research results relate to clinical practice? Can. J. Psychiatry 38 (Suppl. 3), s75–s79.

Malla, A.K., Norman, R.M.G., Scholten, D.J., Zirul, S., Kotteda, V., 2001. A comparison of long-term outcome in first-episode schizophrenia following treatment with risperidone or a typical antipsychotic. J. Clin. Psychiatry 62, 179–184.

McGlashan, T.H., 2001. Psychosis treatment prior to psychosis onset: ethical issues. Schizophr. Res. 51, 47–54.

Merlo, M.C., Hofer, H., Gekle, W., Berger, G., Ventura, J., Panhuber, I., Latour, G., Marder, S.R., 2002. Risperidone, 2 mg/day vs. 4 mg/day, in first-episode, acutely psychotic patients: treatment efficacy and effects on fine motor functioning. J. Clin. Psychiatry 63, 885–891.

Montes, J.M., Ciudad, A., Gomez, J.C., EFESO Study Group, 2003. Safety, effectiveness, and quality of life of olanzapine in first-episode schizophrenia: a naturalistic study. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 27, 667–674.

National Institute of Clinical Excellence, 2002. Schizophrenia: core interventions in the treatment and management of schizophrenia in primary and secondary care. www.nice.org.uk.

Ohlsen, R.I., Jones, H.M., Ohlsen, J.C., Pilowsky, L.S., 2003. Gender differences in response to a weight intervention are not upheld up to twelve months. Schizophr. Res. 60 (Suppl. 1), 364.

Robinson, D., Woerner, M.G., Alvir, J.M.J., Bilder, R., Goldman, R., Geisler, S., Koreen, A., Sheitman, B., Chakos, M., Mayerhoff, D., Lieberman, J.A., 1999. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. Arch. Gen. Psychiatry 56, 241–247.

Sanger, T.M., Lieberman, J.A., Tohen, M., Grundy, S., Beasley Jr., C., Tollefson, G.D., 1999. Olanzapine versus haloperidol treatment in first-episode psychosis. Am. J. Psychiatry 156, 79–87.

Tauscher-Wisniewski, S., Kapur, S., Tauscher, J., Jones, C., Daskalakis, Z.J., Papatheodorou, G., Epstein, I., Christensen, B.K., Zipursky, R.B., 2002. Quetiapine: an effective antipsychotic in first-episode schizophrenia despite only transiently high dopamine-2 receptor blockade. J. Clin. Psychiatry 63, 992–997.

Turgay, A., Binder, C., Snyder, R., Fisman, S., 2002. Long-term safety and efficacy of risperidone for the treatment of disruptive behavior disorders in children with subaverage IQs. Pediatrics 110, e34.

Woods, S.W., McGlashan, T.H., 2002. Adverse effects of olanzapine in adolescents and adults. Schizophr. Res. 53 (Suppl. 170).

World Health Organization, 1992. International Statistical Classification of Diseases and Related Health problems, Tenth Revision, Three Volumes. World Health Organization, Geneva.

Yap, H.L., Mahendran, R., Lim, D., Liow, P.H., Lee, A., Phang, S., Tiong, A., 2001. Risperidone in the treatment of first episode psychosis. Singap. Med. J. 42, 170–173.