1. Strategies of long-term treatment of psychotic disorders

Marek Jarema

Key words: psychotic disorders; long-term treatment; antipsychotics

Summary

Long-term treatment of psychotic disorders requires both the general and the individual approach to the patients and their problems. Such strategies are mainly directed to solve various problems, which not solely are restricted to the medical ones. It is cruicial to determine what are the principal goals for the teratment, as the requirement to resolve psychotic symptoms is not always possible to fulfil. Thus, the description of the treatment staretegies should include the precise definition of treatment goals (remission, recovery, functional improvement, subjective well-being, etc.). The time of treatment needed to reach such a goal is also cruicial. An important role plays the choice of antipsychotic medication, which sometimes leeds to the application of guidelines or teratment algorrithms. Such widely accepted standards are valuable tools to help to identify the most appropriate teratment foir psychotic conditions, being not necessary adequate to patient's expectations and needs.

1.1. Introduction

The majority of patients with psychotic disorders are exposed to the long-term treatment. With the exception of only a selected population of patients who suffer from acute and brief psychotic disturbances mailny caused by specific etiologic factors, the vast majority of people with psychotic disorders require a long-lasting therapeutic support. This means that pharmacotherapy of such patients usually takes place and lasts a substantial period of time. Therefore, there is a need to develop long-term strategies to be implemented in the therapeutic programs aiming at the improvement of health condition of psychotic patients.

By virtue, the term "psychotic disorders" includes schizophrenia and schizophrenia-like disorders as well as bipolar disorders.

The long-term treatment strategy for psychotic patients differs from the therapeutic goals for acute psychotic episodes. Feifel (2002) suggests, that the long-term goals should aim primarily at the improvement of negative symptoms, cognitive function, compliance, and the reduction of side effect burden. One needs to be aware of the fact, that other groups of symptoms are also evident in patients with psychotic disorders. These include, for instance, the obsessive-compulsive psychopathology as well as the cognitive impairment.

However, it needs to be underlined that one of the major factors which indicate the need for extended psychiatric hospitalization for patients with psychotic disorders was the severity of positive symptoms (among other, such like psychological discomfort, resistance BPRS-subscale, and the number of previous hospitalizations) (Hopko et al. 2001). These results indicate, that the long-term therapeutic goal should be the broad clinical improvement, and that the indication of a group of symptoms at which the treatment should aim, may be rather difficult.

The strategies for treatment should be elaborated on the basis of evidence and clinical experience. Research indicate that treatment strategy should have four phases:

- the decision to implement
- initial implementation
- sustained implementation
- termination or transformation
- this also requires organizational changes (Rosenheck, 2001).

It illustrates how complex efforts are needed to develop the strategies for long-term treatment on mental disorders. At the same time one should not forget that patients-oriented point of view has to be seriously considering when

building the strategy to improve psychotic patients' condition. A good example may be the main stategies which are used to "uncovering hope" for the future of schizophrenic patients in the comunity. Such strategies include enhancing motivation and developing pathways to wellness (McCann, 2002).

Modern technology continues to have more substantial impact on the research in psychiatry.

One of many possibilities is the search for a way to base treatment choice on more homogenous psychotic patients' subgroups. The method which may lead to identify such subgroups is to define them through the genetic code (Northup and Nimgaonkar, 2004; Wilffert et al. 2005). However, at present the long-term treatment strategy can not be defined on this kind of scientific findings.

1.2. The definition of the improvement after antipsychotic treatment

The goal of the long-term treatment of psychotic disorders is obviously the support of good clinical improvement, which was achieved during the acute phase of treatment and the establishment or re-establishment of social links that will make it easier for the patients and his/her family to live in the community. In patients suffering from schizophrenia, these goals are sometimes very difficult to achieve, because of the nature of the disease. There are patients in whom a good, satisfatory improvement is quite difficult to expect regardless of the effort we made in order to reach clinical improvement.

Therefore, there is a need for the definition of "improvement" achieved during treatment.

For years, the diminution of most troublesome psychotic symptoms was the main goal of therapeutic efforts. The decrease of the intensity of hallucinations or delusions, the sedation of the aggressive behavior, and more comprehensive verbal contact with the patient, were considered to be the landmarks of imptovement after treatment. Along with the progress of the pharmacological treatment of psychotic disorders, the expectations of satisfactory improvement after treatment raised distinctly. The disappearance of the acute psychotic sympotoms not anymore are considered to be the most important criteria for the improvement. Along with the symptomatic improvement (i.e. the decrease in severity or the elimination of the symptoms), clinitians and

patient's family members wanted to see also social improvement. This means, that by the introduction of modern antipsychotic drugs, the expectation were raised to reach the improvement in patient's social and occupational functioning (Gardner et al. 2005; Jarema et al. 2003; Kane et al. 2000; Lublin et al. 2005; Möller, 2004).

These expectations were generated, in major part, by the progress in psychopharmacology. By the introduction of new antipsychotic drugs, the pharmaceutic companies advertised their products with the support of very specific wording. For instance, the new drugs were announced as those which make patients' life again very active, interesting, promissing indicating that after the initiation of the treatment not only all symptoms of the disease disappear, but the patient returns to his/her normal activity and maintains such a favourable state for the rest of his/her life.

Clinical practice, however, imposes a more sceptic approach to the perspectives of satisfactory improvement after treatment. In the quest for better clinical outcome of the treatment the next step, after symptomatic and social improvement, is the struggle to achieve subjective benefits of terapy. Many members of the therapeutic teams started to realize that there is an urgent need to include patient's subjective well-being as one of the criteria of satisfactory improvement after treatment of psychotic disorders.

Nowadays, the tendency is raising to achieve not only "improvement" after treatment, but rather to reach "remission". It is understandable, that in comparison to, let say, bipolar disorders where clinical remission of symptomatology is quite frequently observed, in psychotic disorders, and expecially in schizophrenia, such a condition like remission is not seen as often as one might expect. The question even is raised whether the remission in schizophrenia is possible to be achieved at all. For years psychiatrists were used to evaluate the possibilities of clinical improvement in schizophrenia as the "rule of 1/3" which means that the treatment results in good improvement in about 30% of patients, reasonable improvement (i.e. ongoing exacerbations and remissions) also in about 1/3 of subjects, and unfavorable outcome (like the persistance of symptoms, inadequate functioning of patients) in remaining 1/3 of those who suffer from schizophrenia.

This rule might be considered as an obsolete one, since the evidence has been shown that even in patients who have reached quite reasonable improvement

(often characterized as "stable" patients) the change of the treatment strategy results in even better improvement.

The good example is the swich of "stable" patients from conventional neuroleptics to second generation antipsychotic drugs given orally or in a long-acting form (Gastpar et al. 2005; Lasser et al. 2005; Nasrallah et al. 2004; van Os et al. 2004).

These examples show that it is always advisable to apply various treatment strategies in order to reach even better improvement during treratment of psychotic disorders. At the same time the struggle for the achievement of more favorable treatment outcome should not disregard the need to maintain the clinical improvement, and thus, to prevent relapse. The natural course of psychosis, schizophrenia for instance, may cause the deterioration of patient's mental state regardless of the efforts we make to maintain clinical improvement. However one of the most important long-term goals is just to prevent the relapse (Möller, 2004).

The prognosis of the treatment outcome is difficult. Variuous clinical features were considered to be the indicators for the remission (the severity of psychotic symptoms, the co-existence of affective symptoms, the presence of disorganized behavior, the time in which the improvement is to be seen, etc). Experts suggests the acute improvement in psychotic symptoms to be the most important predictor of remission (Kane et al. 2000). Other social factors play also an important role. It is expected to link the better treatment outcome to such a condition like good social adjustment, patient's marital status as well as some premorbid personality traits.

1.3. The duration of the antipsychotic treatment

Another factor which need to be taken into consideration when treatment strategies are evaluated, is time. First of all, it has to be underlined that the initiation of the antipsychotic treatment as soon as possible seems to be cruicial for the treatment outcome. The literature proved without any doubt that the initiation of treatment should take place without any delay once the disorder has been diagnosed. Another problem is the treatment of "premorbid" or "prodromal" conditions or symptoms which may indicate that the psychosis will occur while social support and advice may be helpful in such states. The

introduction of pharmacological treatment in such a premorbid state seems to be, at least, questionable.

The so called "duration of untreated psychosis" (DUP) is considered to play the important role in the prognosis of treatment outcome. The majority of authors agree that the shorter is the DUP the greater are the chances for favorable outcome of the disease (Hafner et al. 2004; Malla and Norman, 2001; Malla et al, 2003). The duration of initially unmedicated psychosis proved to be the predictor of impaired adaptive life functioning of schizophrenic patients (Quinn et al. 2001). The early intervention programmes are important not only for more appropriate treatment of patients but for reduction of patients' disability and the costs of care (Carr et al. 2004).

The strategy, therefore, is to improve the diagnostic procedures in order to identify the psychotic disorders as soon as the symptoms have become recognizable. In addition to the reduction of patient's suffering each onset of treatment may also prevent the disruption of social links of the patient so that rehabilitaion and social re-insertion become easier. Obviously this is not an easy task as in many patients the first ever appeared psychotic symtoms are not characteristic (for schizophrenia for instance), rarely indicate the undoubtful psychotic condition, and sometimes even suggest another diagnosis, e.g. affective condition. Very important and also misleading role plays the substance abuse in the great number of patients with first psychotic episode and the strategy aimed at the ruling out the substance-dependent mental conditions is one of the cruicial points on the road to the correct diagnosis and adequate reatment of first episode patients.

Speaking about time one needs to realize that the duration of treatment is another important issue. The clinical guidelines, treatment algorrhythms, or standards, may be very helpful in this matter (Feifel, 2002; Kane et al. 2000; Malla et al. 2003; Mellman et al. 2001).

The requirement of long-term treatment of psychotic disorders is widely supported by such guidelines. Psychiatrists, in general, agree that first psychotic episode should be treated mainly pharmacologically (but other treatment components such as psychotherapy, psychoeducation, and family consultation are also needed) for at least 6 months, but recommended treatment period is one to two years. The suggestions how long should last the treatment of a subsequent psychotic episode are less unanimous because various factors influence the duration of treatment. In general, the treatment of a second

psychotic episode of patients without comorbidity (both mental and somatic) should last at least two years. This period should be extended to the period of "several years" when other mental conditions (affective symptoms/mood disorders, substance-related disorders, cognitive disorders, etc.) are present. The extension of the recommended treatment period is also valid for older patients and those suffering from general medical disorders. The lack of family support as well as difficult living conditions (like homelessness, unemployment, unlawful behavior, etc.) also extend substantially the treatment duration of psychotic disorders. Thus, the strategy should aim also at the improvement of patient's living conditions, the broadening of social support and care offered for those who find themselves in difficult life situations.

1.4. The choice of the antipsychotic medication

The choice of the medication becomes particularily important in the last decade, since the introduction of new antipsychotic drugs (so called second generation antipsychotics, 2GAPs) (Dossenbach et al. 2005; Lalonde, 2003; Lehman, 1999; Tandon and Fleischhacker, 2005). In contrast to the conventional neuroleptics (CNs) the new drugs were supposed to be more efficacious against psychotic symptoms, and better tolerated (DeQuardo and Tandon, 1998; Gardner et al. 2005; Leucht et al. 1999; Lublin et al. 2005; Möller, 2004; Tandon and Jibson, 2004). However, the 2GAPs shoud not be considered as a homogenous group, as they differ anomg thenselves in terms of both clinical efficacy and tolerability (Ananth et al. 2004; Jackson et al. 1999;Jarema et al. 2003). The atypical antipsychotics are now strongly recommended for treatment of psychotic disorders (Kane et al. 2000; The Expert Consensus Guidelines Series, 2003). More than a 10-years lasting clinical experience with the use of 2GAPs in the treatment of psychotic conditions forced the revision of such an enthusiastic expectations linked to the modern antipsychotic medications.

In clinical practive the advantage of 2GAPs over the CNs is to be seen. Several factors favor the newer drugs:

- at least equal efficacy against "positive" symptoms
- better efficacy against "negative" symptoms
- better efficacy agains affective symptoms which accompany psychotic conditions
- more favorable impact on cognitive functions

- better tolerance in terms of extrapyramidal symptoms, as well as other side-effects like symptoms of hyperprolactineamia, or drug-induced hypotonia
- more benefits in terms of "soft" indicators of clinical improvement, such as patients' quality of life, and subjective attitudes toward the treatment
- better compliance with the treatment

There are, however, problems that may be related to the treatment with newer drugs. Regardless of the fact that both patients and psychiatrists consider the 2GAPs as safer than the conventional drugs, troublesome side-effects unfortunately happen during the treatment with new antipsychotics. Despite of the expectations, after the introduction of new antipsychotics, the extrapyramidal symptoms do occur during the treatment with some 2GAPs. These symptoms are less frequently seen during the treatment with the 2GAPs than during conventional neuroleptics treatment but they may be present and require an adjustment of the treatment in terms of dose lowering, concomitant medication with antiparkinsonian drugs, or swich to another antipsychotic (Pierre, 2005).

One of the major problem seems to be the metabolic syndrome (Newcomer, 2004). This condition consists of several symptoms which are considered to be clinically relevant and sometimes may lead to the discontinuation of the treatment. The diagnosis of the metabolic is made when at least 3 of the following symptoms are present: weist >88cm (women) and >102cm (men), triglycerides level > 150 mg/dl, HDL cholesterol level > 50mg/dl (women) and > 40mg/dl (men), blood pressure > 135/85 mmHg, fasting serum glucose > 110 mg/dl (Cassey et al. 2004).

Weight gain during antipsychotic treatment, glucose intolerance, or even diabetes have been reported after 2GAPs treatment, especially after the use of clozapine or olanzapine (Tandon and Jibson, 2001). Several strategies have been proposed to prevent weight gain during antipsychotic treatment, but sometimes the treatment should be changed (Cassey et al. 2004; Newcomer, 2004; Sussman, 2003).

Clinical symtoms of elevated prolactine level (galactorrhea, amenorrhea, sexual dysfunctions, etc.) may result also in the change of the medication in terms of swich to another antipsychotic or the co-administration of drugs which lower the prolactine level, i.e. the dopamine agonists (Malkerson, 2005).

The adequate dosing of 2GAPs is also very important (Kinon et al. 20040. Clinical practice proved that doses recommended by the manufacturer of several 2GAPs are not necessary used in practice. For instance, it is now recommended that risperidone should be used in lower doses than those recommended earlier during registration while olanzapine and quetiapine doses are apparently have to be higher (Citrone and Volavka, 2002).

Thus, the strategy of antipsychotic drug choice include not only the quest for good clinical efficacy but also for good tolerance of the medication.

In the tlong-term treatment a good tolerability of the medication becomes a crucial issue. This is particularly important when the late side-effects of antipsychotics are considered. Among them the tardive diskinesia is one of the most bothersome. Estimated chance for new developed TD in patients under antipsychotic therapy is about 5 % of cases. However this side-effect is significantly less frequent among patients treated with 2GAPs (Correl et al. 2004;Tandon and Jibson, 2001) which needs to be taken into consideration in long-term treatment of psychotic disorders.

Obviously, patient's attitude toward the treatment and the medication plays an important role in planning long-term treatment of psychotic disorders. The choice of the drug should include also consideration of patient's subjective feelings during treatment. These subjective attitudes can influence drug compliance in a great extend. It is estimated, that the adherence to antipsychotic treatment can be ameliorated if the patient considers the treatment as helpful and harmless. Among the factors which promote the compliance with the antipsychotic treatment, the one of the most important is good tolerance of the medication. It has been proved that the presence of troublesome drug-induced side-effects, such as extrapyramidal symptoms or sedation, may reduce treatment adherence in most patients Awad and Voruganti, 2004; McGarth and tempier, 2005; Rattenbacher et al. 2004).

And the co-administration of concomitant medication in order to diminish the dyscomfort caused by the side-effects, should not be considered as an optimal solution. Concomitant medication should be treated as a last possible option in the strategy for antipsychotic treatment. It is always better not to provoke unpleasant side-effects than to tolerate their presence and to be forced to introduce concomitant medication for these symptoms.

Treatment adherence should also be considered in planning long-term antipsychotic treatment strategies. On the basis of the lioterature review Dolder et al.(2003) proved the best improvement of adherence to antipsychotic treatment with the combination of educational, behavioral, and effective strategies. Family education play also an important role, since there is a clear advantage of the family support for the treatment outcome in psychotic disorders in comparison to the situation when patients are deprived any assistance from the part of family members and relatives.

The valuable alternative for long-term treatment of psychotic disorders is the use of long-acting antipsychotics. This treatment releases the patient from the troublesome rutine of taking the medication regularly during the day. It also helps to maintain a stable serum level of neurolepotic drug and obviously improves compliance. Better control of psychotic symptoms and better tolerance of treatment are other advantages of treatment with depot-neuroleptics. The progress on this field has lately been made by the introduction of second gerenation antipsychotic in a long-acting form. Many clinical trials have proved the efficacy of risperidone microspheres in the maintenance treratment of schizophrenia and related disorders which supports the usefullness of long-acting injectible atypical drug in psychotic disorders (Kane et al. 2000; Lasser et al. 2005; Nasrallah et al. 2004; van Os et al. 2004). It needs to be underlined that even stable psychotic patients may benefit, to the large extent, from switching antipsychotic medication to atypical long-acting 2GAP. As mentioned before, patients who were treated with conventional depot neuroleptics and were considered as "stable" improved substantially when their treatment was changed to risperidone-microspheres (Gastpar et al. 2005; Lasser et al. 2005; Nasrallah et al. 2004; van Os et al. 2004). Furthermore, the improvement of patients' mental state (in terms of schizophrenia positive, negative, and general-psychopathology subscales of the PANSS) as well as their quality of life and satisfaction with treatment were seen when the patients were switched from 2GAP – olanzapine – to risperidone microspheres (Gastpar et al. 2005). These results indicate various benefits of long-acting atypical antipsychotic to psychotic patients in the treatment of psychotic disorders wich need to be taken into consideration when planning the long-term treatment.

Atypical long-acting antipsychotc drug is also the alternative for the treatment of older patients with psychosis, because of its good efficacy and tolerability profile (Masand and Gupta, 2003).

Clozapine is a potent antipsychotic which is widely used in clinics to treat psychotic patients. Its efficacy has been proved since its introduction in Europe some 30 years ago, and since that time this drug is considered as the only one with proved efficacy in so-called drug-resistant psychoses (mainly schizophrenia) (Ahn et al. 2005; Ananth et al. 2004; Brambilla et al. 2002; Gaszner and Makkos, 2004; Wahlbeck et al. 2000). Patients also benefit from long-lasting antipsychotic treatment with clozapine in comparison to conventional treatment (Ananth et al. 2004; Wahlbeck et al. 2000), not only in terms of clinical improvement but also in terms of the reduction of the number of hospital admissions, the lenght of hospitalizations as well as the reduction of the potential risk for suicide (ahn et al. 2005).

However the revision of clozapine's efficacy and tolerability in comparison to the conventional drugs and to new atypical drugs gives mixed results (Brambilla et al. 2002; Gaszner and Makkos, 2004; Tuunainen et al. 2001). Gaszner and Makkos (2004) after the review of over 1000 medical records of patients treated with clozapine for years (the mean duration of treatment was 12.2 years and the mean clozapine dose was 71.5 mg daily) found clozapine to be efficacious in various types of schizophrenia, however the relaps rate was similar to that observed in patients treated with haloperidol. In this report the authors found clozapine to be better tolerated than conventional antipsychotic.

1.5. Conclusions

The strategies of long-term treatment of various psychotic disorders require the overwie of the currently available possibilities. This includes not only the thorough definition of improvement after treatment but also the establishing of the time-frame for the treatment as well as the choice of the medication which is most appropried to the particular patient and the clinical conditions. It seems to be quite convincing the the treatment strategy tailored to patient's individual needs constitutes the optimal approach to the long-term treatment of psychotic disorders.

Lately, the vigorous discussion has been proveked by the publication of the CATIE study (Lieberman et al. 2005) which raised the issiue of the various antipsychotics efficacy in chronic codition (in schizophrenia). This discussion, and in particular, the indication for the possible bias in this trial (like for instance the question of the adequate dosing of antipsychotic medications

used) shows how vulnerable may be some arguments in favor of particular antipsychotic treatment. In the present monography we try to overcome tuch a potential bias by putting the emhasis on the general view rather that identifying potential "best treatment" for certain psychotic condition. Thus, the strategies are focused on the patient and on the optimization of care rather than on the technical aspects of the pharmacological treatment.

1.6. References

1. Ahn YM, Chang JS, Kim Y, Lee KY, Kim JH, Kim SC, Maeng SJ, Kim YS. Reduction in hospital stay of chronic schizophrenic patients after long-term clozapine treatment. Itl Clin Psychopharmacol. 2005; 20: 157-161.
2. Ananth J, Para,eswaran S, Hara B. Drug therapy in schizophrenia. Curr Pharm Des. 2004; 10: 2205-2217.
3. Awad AG, Voruganti LN: Impact of atypical antipsychotics on quality of life in patients with schizophrenia. CNS Drugs. 2004; 18: 877-893.
4. Brambilla P, Barale F, Caverzasi E, Tognoni G, Barbui C. Clozapine-treated subjects with treatment-resistant schizophrenia: a systematic review of experimental and observational studies. Int Clin Psychopharmacol. 2002; 17: 189-195.
5. Carr VJ, Lewin TJ, Neil AL, Halpin SA, Holmes S: Premorbid, psychosocial and clinical predictors of the costs of schizophrenia and other psychoses. Br J Psychiatry. 2004; 184: 517-525.
6. CasseyDE, Haupt DW, Newcomer JW, Henderson DC, Sernyak MJ, Davidson M, et al. Antipsychotic-induced weight gain and metabolic abnormalities: implications for increased mortality in patients with schizophrenia. J Clin Psychiatry. 2004; 65, Suppl. 18: 36-46.
7. Citrome L, Volavka J. Optimal dosing of atypical antipsychotics in adults: a review of the current state. Harv Rev Psychiatry. 2002; 10: 280-291.
8. Correll CU, Leucht S, Kane JM: Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. Am J Psychiatry. 2004; 161: 414-425.
9. DeQuardo JR, Tandon R: Do atypical antipsychotic medications favorably alter the long-term course of schizophrenia? J Psychiatr Res. 1998; 32: 229-242.
10. Dolder CR, Lacro JP, Leckband S, Jeste DV. Interventions to improve antipsychotic medication adherence: review of recent literature. J Clin Psychiatry. 2003; 23: 389-399.
11. Dossenbach M, Arango-Davilla C, Silva Ibarra H, Lanada E, Aguilar J, Caro O, Leabbetter J, Assuncao S: Response and relapse in patients with schizophrenia treated with olanzapine, risperidone, quetiapine or haloperidol: 12 months follow-up of the International Schizophrenia Outpatient Health Outcomes (IC_SOHO) Study. J Clin Psychiatry. 2005; 66: 1021-1030.
12. Feifel D: Rationale and guidelines for the inpatient treatment of acute psychosis. J Clin Psychiatry. 2000; 61, Suppl 14:27-32.
13. Gardner DM, Baldessarini RJ, Waraich P: Modern antipsychotic drugs: a critical overview. C M A J. 2005, 172: 1703-1711.
14. Gastpar M, Masiak M, Latif MA, Frazzingaro S, Medori R, Lombertie ER: Sustained improvement of clinical outcome with risperidone long-acting injectable in psychotic patients previously treated with olanzapine. J Psychopharmacol. 2005; 19, Suppl. 5: 32-38.

15. Gaszner P, Makkos Z: Clozapine maintenance therapy in schizophrenia. Prog. Neuropsychopharmacol. Biol Psychiatry. 2004; 28: 465-469.
16. Hafner H, Maurer K, Ruhrmann S, Bechdolf A, Klosterkotter J, Wagner M, Maier W, Bottlender R, Moller HJ, Gaebel W, Wolwer W: Early detection and secondary prevention of psychosis: facts and visions. Eur Arch Psychiatry Clin Neurosci. 2004; 254: 117-128.
17. Hopko DR, Lachar D, Bailey SE, Varner RV: Assessing predictive factors for extended hospitalization at acute psychiatric admission. Psychiatr Serv. 2001; 52:1367-1373.
18. Jackson DM, Dursun S, Denovan-Wright EM. Recent advances in potential atypical antipsychotics: past, present and future hopes – preclinical and clinical considerations. I. Drugs; 1999; 2: 886-895.
19. Jarema M., Rybakowski J, Landowski J.: Second generation antipsychotics: similarities and differencies. Psychiatr Pol. 2003; 37: 7-28.
20. Kane JM, Leucht S, Carpenter D, Docherty JP. Expert consensus guideline series. Optimizing pharmacologic treatment of psychotic disorders. Introduction: methods, commentary, and summary. J Clin Psychiatry. 200; 64, Suppl 12: 5-19.
21. Kinon BJ, Ahl J, Stauffer VL, Hill AL, Buckley PF: Dose response and atypical antipsychotics in schizophrenia. CNS Drugs. 2004, 18: 597-616.
22. Lalonde P: Evaluating antipsychotic medications: predictors of clinical effectiveness. Report of an expert panel efficacy and effectiveness. Can J Psychiatry. 2003; 48, Suppl. 1: 3S-12S.
23. Lasser RA, Bossie CA, Gharabawi GM, Baldessarini RJ: Clinical improvement in 336 stable chronically psychotic patients changed from oral to long-acting risperidone: a 12-month open trial. Int J Neuropsychopharmacol. 2005; 8: 427-438.
24. Lehman AF: Developing an outcomes-oriented approach for the treatment of schizophrenia. J Clin Psychiatry. 1999; 60, (Suppl) 19:30-35.
25. Leucht S, Pitschel-Walz G, Abraham D. Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics ad placebo: a meta-analysis of randomized controlled trials. Schizophr Res, 1999; 35: 51-68.
26. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK, Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005; 353:1209-23.
27. Lublin H, Eberhard J, Levander S: Current therapy issues and unmet clinical needs in the treatment of schizophrenia: a review of the new generation antipsychotics. Itl Clin Psychopharmacol. 2005; 20: 183-198.
28. Malkerson K: Differences in prolactin elevation and related symptoms of atypical antipsychotics in schizophrenic patients. J Clin Psychiatry. 2005; 66: 761-767.
29. Malla AM, Norman RM: Treating psychosis: is there more to early intervention than intervening early? Can J Psychiatry. 2001; 46: 645-648.
30. Malla A, Norman R, McLean T, Scholten D, Townsend L. A Canadian progremme for early intervention in non-affective psychotic disorders. Aust N Z J Psychiatry. 2003; 37: 407-413.
31. Masand PS, Gupta S: Long-acting injectable antipsychotics in the elderly: guidelines for effective use. Drugs Aging. 2003; 20: 1099-1110.
32. McCann TV. Uncovering hope with clients who have psychotic illness. J Holist Nurs. 2002; 20: 81-99.
33. McGrath BM, Tempier RP: Patients' opinions of olanzapine and risperidone following long-term treatment: results from a cross-sectional survey. Pharmacopsychiatry. 2005, 38: 147-157.
34. Mellman TA, Miller AL, Weissman EM, Crismon ML, Essock SM, Marder SR: Evidence-based pharmacologic treatment for people with severe mental illness: a focus on guidelines and algorithms. Psychiatr Serv. 2001; 52: 619-625.

35. Möller HJ: Course and long-term treatment of schizophrenic psychoses. Pharmacopsychiatry. 2004; 37, Suppl. 2: 126-135.
36. Möller HJ: Novel antipsychotics in the long-term treatment of schizophrenia. World J. Biol. Psychiatry. 2004, 5: 9-19.
37. Nasrallah HA, Duchesne I, Mehnert A, Janagap C, Eerdekens M. Health-related quality of life in patients with schizophrenia during treatment with long-acting, injectable risperidone. J Clin Psychiatry. 2004; 65: 531-536.
38. Newcomer JW: Metabolic risk during antipsychotic treatment. Clin Ther. 2004, 26: 1936-1946.
39. Northup A, Nimgaonkar VL. Genetics of schizophrenia: implications for treatment. Expert Rev Neurother. 2004; 4: 725-731.
40. Pierre JM: Extrapyramidal symptoms with atypical antipsychotics: incidence, prevention and management. Drug Saf. 2005; 28: 191-208.
41. Quinn J, Moran M, Lane A, Kinsella A, Waddington JL: Long-term adaptive life functioning in relation to initiation of treatment with antipsychotics over the lifetime trajectory of schizophrenia. Biol Psychiatry. 2000; 48: 163-166.
42. Rattenbacher MA, Burns T, Kemmler G, Fleischhacker WW: Schizophrenia: attitudes of patients and professional carers toward the illness and antipsychotic medication. Pharmacopsychiatry. 2004; 37: 103-109.
43. Rosenheck R: Stages in the implementation of innovative clinical programs in complex organizations. J Nerv Ment Dis. 2001; 189: 812-821.
44. Sussman N: The implications of weight changes with antipsychotic treatment. J. Clin. Psychopharmacol. 2003, 23: S21-S26.
45. Tandon R, Jibson MD. Pharmacologic treatment of schizophrenia: what the future holds. CNS Spectr. 2001; 6: 980-986.
46. Tandon R, Fleischhacker W. Comparative efficacy of antipsychotics in the treatment of schizophrenia: a critical assessment. Schizophr Res. 2005, 79: 145-55.
47. The Expert Consensus Guidelines Series: Optimizing pharmacologic treatment of psychotic disorders. J Clin Psychiatry. 2003, 64, Suppl. 12.
48. Tuunainen A, Wahlbeck K, Gilbody S. Newer atypical antipsychotic medication in comparison to clozapine: a systematic review of randomized trials. Schizophr Res. 2002; 56: 1-10.
49. van Os J, Bossie CA, Lasser RA: Improvements in stable patients with psychotic disorders switched from oral conventional antipsychotics therapy to long-acting risperidone. Int Clin Psychopharmacol 2004; 19: 229-232.
50. Wahlbeck K, Cheine M, Essali MA: Clozapine versus typical neuroleptic medication for schizophrenia. Cochrane Database Syst Rev, 2000; 2: CD00059.
51. Wilffert B, Zaal R, Brouwers JR. Pharmacogenetics as a tool in the therapy of schizophrenia. Pharm World Sci. 2005; 27: 20-30.