

Long-term pharmacotherapy of schizophrenic patients: Achievements, unsolved needs and future perspectives with special focus on long-acting injectable second generation antipsychotics

Hans-Jürgen Möller

Summary

Schizophrenia is a disorder with a poor long-term outcome. Second generation antipsychotics (SGAs) offer some better treatment options for patients suffering from schizophrenia in terms of a broader efficacy profile and reduced risks of extrapyramidal side effects (EPS). However, in the long-term treatment conditions the problem of a high non-adherence rate has not been resolved sufficiently. The introduction of depot formulations of SGAs might serve as an option to further improve the situation. The respective data of long-acting injectable risperidone are reviewed. Future perspectives of a broader indication of this approach are discussed.

Schizophrenia / second generation antipsychotics / efficacy profile / long-term treatment / long-acting injectable depot formulation

INTRODUCTION

Schizophrenia is a major psychotic disorder or a cluster of disorders which usually appears first in late adolescence or early adulthood. The psychopathological symptoms are not only present during the acute episodes, but develop to a chronic condition in a high proportion of patients. Consequences are impairments of occupational and social functioning [1, 2, 3]. Despite

improvement in the treatment of schizophrenia, it still presents an enormous burden to the patients and their relatives [4, 5]. Additionally, direct and indirect health costs are high. Considering these facts it seems necessary to offer the best treatment possible to individuals suffering from schizophrenia.

Treatment with Antipsychotics: FGAs vs. SGAs

Antipsychotics have formed the basis of schizophrenia treatment for approximately 50 years. In terms of their chemical structure, the antipsychotics, traditionally called neuroleptics, are a heterogeneous group of psychoactive drugs and include phenothiazines, thioxanthenes, butyrophenones, diphenylbutylpiperidines, benzamides, benzisoxazoles and dibenzepines. They are used in the acute phase treatment as well as for long-term treatment/prevention of relapses [6, 7]. Traditional/conventional neuroleptics, also called first-generation antipsychotics (FGAs), can

Hans-Jürgen Möller: Chairman, Department of Psychiatry, Ludwig-Maximilians-University München, Nussbaumstrasse 7 80336 Munich, Germany. Correspondence address: Department of Psychiatry, Ludwig-Maximilians-University München, Nussbaumstrasse 7 80336 Munich, Germany. E-mail: hans-juergen.moeller@med.uni-muenchen.de

Conflict of Interest - Financial Disclosure Statement: Prof. Dr. Moeller has received grants or is a consultant for and on the speakership bureaus of AstraZeneca, Bristol-Myers Squibb, Eisai, Eli Lilly, GlaxoSmithKline, Janssen Cilag, Lundbeck, Merck, Novartis, Organon, Pfizer, Sanofi-Aventis, Schering-Plough, Schwabe, Sepracor, Servier and Wyeth.

be classified into high- and low-potency medications. The effective dose of a first-generation antipsychotic medication is closely related to its affinity for dopamine receptors (particularly D2) and its tendency to cause EPS [6, 8]. High-potency antipsychotics have a greater affinity for D2 receptors than low-potency medications and the effective dose required to treat psychotic symptoms like delusions and hallucinations is much lower than for low-potency antipsychotics. This dose relationship can be expressed in terms of dose equivalence (e.g., 100 mg of low-potency antipsychotic chlorpromazine has an antipsychotic effect that is similar to that of 2 mg of the high-potency antipsychotic haloperidol). Dose equivalence does not equate with equivalence of tolerability and should be considered as a general concept rather than a precise clinical guide. Sedation and orthostatic hypotension are reasons for which doses of low-potency antipsychotics with a sufficient antipsychotic effect can often not be reached.

With the detection of clozapine as an effective antipsychotic agent that does not induce EPS, a new class of antipsychotics, the atypical antipsychotics, became established. Because various modern antipsychotics can be found on a continuum ranging from typical to atypical, the terminus second generation antipsychotics (SGAs) for describing these new agents, which induce considerably less EPS in a therapeutic dose range than conventional neuroleptics, has been found to be more suitable than the synonymously used term 'atypical antipsychotics' [9, 10].

Generally speaking, the SGAs have a lower liability to induce EPS [11], although methodological limitations of the respective RCT might inflate the size of the advantage [12] and still sufficient long-term data on the lower risk of tardive dyskinesia (TD) are missing [13, 14, 15, 16]. On the other side the problem of weight gain and related metabolic issues gained increasing awareness in the context of the development of SGAs [17, 18]. However, this does not seem to be the problem of all SGAs but a risk of some single SGAs. It is not finally resolved why Clozapine and Olanzapine for example have a higher risk, whereas ziprasidone has no or only a low risk [19]. Altogether, there is an increasing consensus that there exists a huge variance between

single SGAs and that it might be better to focus more on single SGAs [20, 21].

In the most recent meta-analysis including 150 double-blind mostly short-term studies with 21533 patients [21] the following results were obtained: Four of these drugs were better than FGAs for overall efficacy, with small to medium effect sizes (amisulpride -0.31 [95% CI -0.44 to -0.19 , $p < 0.0001$], clozapine -0.52 [-0.75 to -0.29 , $p < 0.0001$], olanzapine -0.28 [-0.38 to -0.18 , $p < 0.0001$], and risperidone -0.13 [-0.22 to -0.05 , $p = 0.002$]). The other second-generation drugs were not more efficacious than the FGAs, not even for negative symptoms. Second-generation antipsychotic drugs induced fewer EPS than did haloperidol (even at low doses). Only a few have been shown to induce fewer EPS than low-potency FGAs. With the exception of aripiprazole and ziprasidone, second-generation antipsychotic drugs induced more weight gain, in various degrees, than did haloperidol but not than low-potency FGAs.

Limitations in relapse preventions with antipsychotics

There is clear evidence that a continuous medication with antipsychotics can reduce the risk of relapse significantly. This has been demonstrated by several randomised placebo-controlled double blind trials [22, 23]. Most of the placebo-controlled studies on neuroleptic relapse prophylaxis with oral neuroleptics were performed between 1970 and 1985. They cover a maximum time span of two years, since longer treatment under placebo conditions is hard to realise for various reasons. Several simple or placebo-controlled discontinuation studies have shown that after long-term neuroleptic medication of up to two years, in one study even three years, there is still a considerable risk of relapse, which can be significantly reduced by continuation of the neuroleptic medication. The study by Cheung [24] is of interest in this context due to its long study period. He found that in patients who had received successful relapse-prophylactic treatment with neuroleptics for three to five years, 62% of those who were then given placebo suffered relapse in the subsequent years while only 13% of

those who continued to receive neuroleptics suffered a relapse.

A huge problem especially of long-term treatment is the high proportion of non-compliance. The majority of patients discontinues treatment at some point due to loss of motivation, often associated with increasing sensibility to side effects. The problem of non-compliance [25, 26] was described already in the context of the early control-group studies to evaluate relapse prevention with oral neuroleptics. Hogarty et al. [27] pointed out that approximately 50% of patients had discontinued their medication prematurely. This observation in control-group studies must apply to an even greater degree to routine treatment. There was hope that the use of SGAs would overcome this problem in a relevant way and that SGAs generally would demonstrate better efficacy results. Although this is partially true, the advantage of the SGAs amounts only to a 10% difference in relapse prevention, as demonstrated in the respective meta-analysis by Leucht et al. [28].

Given the fact that non-compliance can be seen as a major cause of relapse there is no doubt that non-compliance is a huge burden on the patients and their relatives, but also on society in general. Financially, the costs of non-compliance are significant, with an estimated 40% of total costs of the illness [29]. Given the fact that apparently the preferential use of SGAs cannot overcome to a satisfactory degree the problems of non-compliance [30, 31, 32], the question arises whether depot neuroleptics are more successful at guaranteeing compliance.

The advantages of depot formulations and the advent of long-acting injectable risperidone

The recently published results of a huge North American multi-centre effectiveness trial on neuroleptic treatment CATIE [33] as well as the European EUFEST study [34] demonstrated the high proportion of discontinuation under maintenance treatment with oral atypical neuroleptics, even under clinical trial conditions and, as to the EUFEST results, even for first episode patients. This challenge of a high discontinuation rate, even with atypical neuroleptics, has to be answered by alternative treatment strategies. In this context, the niche indication of classical depot neuroleptics might possibly be replaced by

a meaningfully broader indication of injectable long-acting SGAs.

The general results of two meta-analyses on trials testing FGA's depot formulations [35, 36], that the superiority in relapse prevention can hardly be demonstrated in such control group studies, is disappointing and, in particular, does not fit to the positive experiences with depot neuroleptics in clinical practice [37]. This was explained by the assumption that it is extremely difficult to demonstrate in the context of a controlled clinical trial the superiority of the depot neuroleptics, because the study procedure itself overestimates the compliance under the oral condition, while at the same time underestimating the advantages of the long-acting formulation. Despite these results, based on clinical experience depot antipsychotic preparations appear useful in relapse prevention when used for patients who have difficulties with medication compliance [7].

For a long time only depot formulations of conventional neuroleptics were available, with their high risk of EPS. There was therefore only very restricted use of depot neuroleptics, which mainly focussed on chronic patients who were difficult to treat and had a high risk of non-compliance. The situation might change with the advent of depot formulations of atypical neuroleptics.

To date, two long-acting injectable SGAs have been developed and undergone randomised controlled clinical trials (RCTs) for the treatment of schizophrenia: risperidone long-acting injectable (RLAI) [38] and olanzapine pamoate (OP) [39, 40, 41, 42]. Since 2002 RLAI is approved and available in Europe and the United States for maintenance treatment of adult patients with schizophrenia, sufficiently stabilised with antipsychotics during acute treatment. Extensive post-marketing experience and data are available for RLAI, with an estimated exposure of 678,000 patient-years since 2001 [42]. The European authority EMA approved OP in November 2008 for maintenance treatment of adult patients with schizophrenia sufficiently stabilised during acute treatment with oral olanzapine. The labelling requires 3 hours of observation for post-injection delirium sedation syndrome (PDSS) in a healthcare facility by appropriately qualified personal after each OP administration for signs and symptoms consistent with olanzapine over-

dose [43]. So far, the clinical experiences with olanzapine pamoate are limited in comparison to long-acting injectable risperidone. Therefore, only the latter compound will be focussed on in the next chapter.

Risperidone long-acting injectable (RLAI): effective for long-term treatment of schizophrenia patients

There is a broad database of evidence demonstrating efficacy of risperidone in treating the acute schizophrenia episode, and showing a more favourable EPS tolerability profile than conventional neuroleptics, especially in the lower dose range [11, 44]. Beside the efficacy and tolerability data for the acute schizophrenic episode, data from a well-designed relapse-prevention study are also available, demonstrating the advantage of risperidone over haloperidol [45]. Additionally, the positive results of the similarly designed first onset schizophrenia study have to be mentioned here [46]. Risperidone has certain advantages and disadvantages compared to other second generation antipsychotics, which may be especially relevant in the treatment of individual patients [44]. As risperidone does not completely lack the risk of inducing EPS, the dose should be kept as low as possible.

Two double-blind, randomised phase III studies, one versus placebo and the other versus oral risperidone, have demonstrated antipsychotic efficacy for long-acting injectable risperidone. These two studies, together with one open-label, long-term study (12 months), belong to the core group of trials that were relevant for the licensing of long-acting risperidone (for details of these and other relevant studies see the reviews of [38, 43]. The two randomised control group studies on acute patients, one versus placebo [47] the other versus oral risperidone RLAI [48], demonstrated the efficacy of risperidone RLAI in terms of superiority to placebo and in terms of equivalent efficacy to oral risperidone under short-term conditions. The 12-month, open-label trial of long-acting injectable risperidone included a large number of schizophrenic and schizoaffective patients (15.2% of the sample). The findings in the total of 725 schizophrenic patients (n=615) were published by Fleischhacker et al. [49], suggesting positive conclusions about

the efficacy, tolerability and utility of long-acting injectable risperidone. The 12-month trial was completed by 65% of patients. Treatment was discontinued because of adverse events in only 5% of patients. A substantially higher proportion of patients in the 75mg group discontinued because of insufficient response: 15% versus 2% in the 25mg group and 3% in the 50mg group. Symptom severity (PANSS total scores) and severity of positive and negative symptoms were reduced from baseline to endpoint in each of the dose groups. According to both the LOCF analysis and observed case analysis, the improvements were significant in each group. Greater improvements were seen in the 25mg and 50mg groups than in the 75mg group.

A relapse prevention control group study comparing the long-acting formulation vs. oral risperidone was not performed given the principal methodological problems and pitfalls of such a comparison mentioned above. Instead of proceeding in this direction, an attempt was made to collect as much clinical data as possible from observational studies that investigated practically relevant questions, amongst others [50, 51, 52, 53, 54]. Some of these studies will be described below.

Post hoc, the recently proposed remission criteria for schizophrenia [55] were applied to the whole sample of the 12-months study [51]. Groups were identified by initial remission status. Although considered clinically stable, 68.2% did not meet the symptom-severity component of remission criteria at baseline. Following long-acting, injectable risperidone treatment, 20.8% of non-remitted patients at baseline achieved symptom remission for at least 6 months. Among 31.8% of patients meeting the symptom-severity component of remission criteria at baseline, 84.8% maintained these criteria at endpoint. A similar approach was used by Emsley et al. [56] in an open-label trial of risperidone RLAI in patients with recent onset of schizophrenia. In this two-year open trial a huge remission rate and a low relapse rate were found.

A recent post-hoc comparison of two long-term studies on early schizophrenia, one using injectable, long-acting risperidone, the other using oral risperidone or haloperidol, has reported significantly more discontinuation with either oral agent vs. injectable after 1 year (49% with

oral vs. 20% with injectable, $p < 0.005$) and 2 years (70% oral vs. 26% injectable, $p < 0.005$) [57]. Discontinuation rates were similar with both oral agents.

In a small, 2-year, naturalistic study of 55 consecutive patients with first-episode schizophrenia assigned to risperidone as either an oral or long-acting injectable formulation, partial or non-adherence occurred for 68% treated with oral risperidone and 32% with long-acting injectable risperidone ($p = 0.01$) [58].

More recently, data from the Schizophrenia Treatment Adherence Registry (e-STAR) prospective, observational survey of patients with schizophrenia have provided treatment retention data for patients initiated on long-acting injectable risperidone formulation or an oral SGA and followed for 2 years [59]. SGAs were most commonly olanzapine (37%) and risperidone (36%). At 24 months, treatment retention was significantly higher with long-acting injectable risperidone than oral SGAs (82% vs. 63%, $p < 0.0001$).

Clinical benefits of using long-acting therapies with better adherence was supported by a review of studies comparing 1-year relapse with oral versus injectable antipsychotics, reporting substantially more relapse with oral therapy (42% vs. 27%) [60].

An open-label, randomised, active-controlled, 2-year trial evaluated 710 patients with schizophrenia or related disorders who were switched from stable treatment with oral risperidone, olanzapine, or conventional neuroleptics to risperidone long-acting injectable (RLAI) or oral quetiapine. Primary effectiveness evaluation was time-to-relapse. Safety evaluations included adverse events (AEs) reported for the duration of the study, Extrapyramidal Symptom Rating Scale (ESRS), clinical laboratory tests, and vital signs. A total of 666 patients ($n = 329$ RLAI, $n = 337$ quetiapine) were evaluable for effectiveness measures. Baseline demographics were similar between treatment groups. Kaplan-Meier estimate of time-to-relapse was significantly longer with RLAI ($p < 0.0001$). Relapse occurred in 16.5% of patients with RLAI and 31.3% with quetiapine [61].

Risperidone long-acting injectable: safety aspects

Based on the available data, RLAI 25 mg, 37.5 mg, and 50 mg generally appeared to be well tolerated [42]. Unwanted effects [62] were similar to those known from treatment with oral risperidone [44]. Also the frequency and severity were generally the same size [43]. RLAI has been associated with an incidence of EPS similar to that with oral risperidone, with AEs appearing to be dose related. Studies consistently found the frequency and severity of EPS to be significantly reduced over time with RLAI treatment [49, 54, 63]. Consistent with other SGAs, RLAI was associated with a low incidence of treatment-emergent tardive dyskinesia (1.2% annually) in one study [64]. This study also reported a significant reduction in the mean score on the ESRS physician's examination for dyskinesia ($p < 0.001$), although further long-term studies are required to explore this potential. Moreover, in some of the clinical trials, patients were switched to RLAI without a significant increase in the risk for or severity of EPS. This included patients switched from conventional oral and long-acting antipsychotic agents to RLAI without the use of transitional oral risperidone [54, 65]. Weight gain with RLAI was in the range from 1 to 2 kg in the short term (12 weeks) [47, 54] and ~ 3 kg after 1 year of treatment, with no further weight gain apparent in patients receiving RLAI for up to 4 years [66]. In the patient populations studied, including antipsychotic injection-naïve patients, the perception of pain at the RLAI injection site was rated as mild and decreased over time [50, 67, 68]. Recently, a deltoid application of risperidone LAI was introduced. Although it could not show clear advantages in terms of tolerability, many patients might still prefer this injection location for several reasons [69].

Clinical perspectives for clinical use of long-acting injectable SGAs

The described problem of a high discontinuation rate, even with SGAs, has to be answered by alternative treatment strategies. In this context, the niche indication of classical depot neuroleptics might possibly be replaced by a broader indication of long-acting SGAs [70, 71, 72]. When

considering broadening the indication of long-acting injectable SGAs, even first-episode patients should be included, who are also known to have a high degree of non-compliance [56, 57, 73, 74].

In order to really benefit from the potential of a long-acting atypical antipsychotic it also seems worthwhile to think about starting treatment with a long-acting formulation earlier than used to be the rule. Especially in countries where the duration of hospital stay for the treatment of acute schizophrenic episodes is comparatively short, it might make sense to start the long-term treatment at a very early stage before discharge in order to guarantee compliance after discharge from hospital. But such a strategy might even be meaningful under other conditions, i.e. in countries where the hospital stay for a schizophrenic episode is quite long, potentially also with the goal to achieve an earlier discharge from hospital, knowing that compliance is guaranteed. More data is required that supports this early treatment strategy with long-acting formulations of atypical neuroleptics.

Despite the high incidence of medication non-compliance [70, 75], many clinicians may be reluctant to consider administering long-acting injectable antipsychotics [30, 76]. Due to the traditional situation with classical depots, long-acting antipsychotics may be perceived as a treatment of last resort that is to be given only after multiple relapses. Clinicians may fear that adverse effects, such as acute dystonia or neuroleptic malignant syndrome, which were common in the period of the classical neuroleptics, may be prolonged and difficult to manage with long-acting agents. However, the good tolerability of the SGAs has changed the situation. Psychiatrists have to learn that long-acting injectable SGAs offer more treatment opportunities than the classical depots, and they should consider this potential when making their treatment decisions. Long-acting injectable atypicals should not be restricted to the indication of patients with a history of poor adherence or to minimise covert non-compliance. They might offer the opportunity to achieve better treatment outcome in a much larger group of patients. The recent evidence about efficacy of long-acting risperidone in patients with schizophrenia and a co-morbidity of substance abuse [53] serves as a valuable

example for a beneficial broader application of long-acting SGAs. The high prevalence of co-occurring substance abuse or addiction in schizophrenia (15-65% [77], the lack of data about the use of depot formulations in this indication, and the negative implications for the course of schizophrenia should stimulate researchers to conduct further trials using long-acting second-generation antipsychotics in this population.

The patient's subjective dimension of clinical decision-making also deserves consideration. There are various pros and cons for a patient's decision about treatment with a depot neuroleptic. These include a fear of stigmatisation associated with depots of classical neuroleptics, which are seen as being a treatment for poor outcome patients. On the other side, the fact that only one injection is required every 2 to 4 weeks, instead of taking a pill once or several times a day, is seen as a pragmatic advantage [78].

REFERENCES

1. Bottlender R, Strauss A, Moller HJ. Social disability in schizophrenic, schizoaffective and affective disorders 15 years after first admission. *Schizophr Res.* 2010; 116: 9–15.
2. Möller HJ, Jager M, Riedel M, Obermeier M, Strauss A, Bottlender R. The Munich 15-year follow-up study (MUFSSAD) on first-hospitalized patients with schizophrenic or affective disorders: Assessing courses, types and time stability of diagnostic classification. *Eur Psychiat.* 2010a.
3. Möller HJ, Jager M, Riedel M, Obermeier M, Strauss A, Bottlender R. The Munich 15-year follow-up study (MUFUSSAD) on first-hospitalized patients with schizophrenic or affective disorders: comparison of psychopathological and psychosocial course and outcome and prediction of chronicity. *Eur Arch Psy Clin N.* 2010b; 260: 367–384.
4. Möller-Leimkühler A. Multivariate prediction of relatives' stress outcome one year after first hospitalization of schizophrenic and depressed patients. *Eur Arch Psy Clin N.* 2006; 256: 122–130.
5. Schennach-Wolff R, Jager M, Seemuller F, Obermeier M, Messer T, Laux G, Pfeiffer H, Naber D, Schmidt LG, Gaebel W et al. Defining and predicting functional outcome in schizophrenia and schizophrenia spectrum disorders. *Schizophr Res.* 2009; 113: 210–217.
6. Falkai P, Wobrock T, Lieberman J, Glenthøj B, Gattaz WF, Moller HJ. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, Part 1: acute treatment of schizophrenia. *World J Biol Psychiat.* 2005; 6: 132–191.

7. Falkai P, Wobrock T, Lieberman J, Glenthøj B, Gattaz WF, Møller HJ. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, Part 2: long-term treatment of schizophrenia. *World J Biol Psychiat*. 2006; 7: 5–40.
8. Creese I, Burt DR, Snyder SH. Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. *Science*. 1976; 192: 481–483.
9. Fleischhacker WW. Second generation antipsychotics. *Psychopharmacology (Berl)*. 2002; 162: 90–91.
10. Möller HJ. Definition, psychopharmacological basis and clinical evaluation of novel/atypical neuroleptics: methodological issues and clinical consequences. *World J Biol Psychiatry*. 2000a; 1: 75–91.
11. Möller HJ, Riedel M, Jäger M, Wickelmaier F, Maier W, Kuhn KU, Buchkremer G, Heuser I, Klosterkötter J, Gastpar M et al. Short-term treatment with risperidone or haloperidol in first-episode schizophrenia: 8-week results of a randomized controlled trial within the German Research Network on Schizophrenia. *Int J Neuropsychop*. 2008; 11: 985–997.
12. Tandon R, Belmaker RH, Gattaz WF, Lopez-Ibor JJ, Jr., Okasha A, Singh B, Stein DJ, Olie JP, Fleischhacker WW, Moeller HJ. World Psychiatric Association Pharmacopsychiatry Section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia. *Schizophr Res*. 2008; 100: 20–38.
13. Chouinard G. Effects of risperidone in tardive dyskinesia: an analysis of the Canadian multicenter risperidone study. *J Clin Psychopharmacol*. 1995; 15: 36S–44S.
14. 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 Psychiat*. 2004; 161: 414–425.
15. Gerlach J. Improving outcome in schizophrenia: the potential importance of EPS and neuroleptic dysphoria. *Ann Clin Psychiatry*. 2002; 14: 47–57.
16. Llorca PM, Devos E, Eerdekens M, et al. Re-hospitalization rates with long-acting risperidone injection are lower than those reported for other antipsychotics. *Int J Neuropsychop*. 2002; 5 (Suppl 1): 189.
17. American Psychiatric Association. Practice guidelines for the treatment of patients with schizophrenia. 2nd ed. *Am J Psychiat*. 2004; 161(Suppl 2): 1–114.
18. De Hert M, Dekker J, Wood D, Kahl K, Möller HJ. Cardiovascular disease and diabetes in people with severe mental illness: Position Statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). *Eur Psychiat*. 2009; 24: 412–424.
19. Möller HJ, Riedel M. Side effect burden of antipsychotic medication. In: Kasper S, Papadimitriou GN, editors. *Schizophrenia. Biopsychosocial Approaches and Current Challenges*. Second ed. London, Informa Healthcare. 2009. p. 231–259.
20. Leucht S, Pitschel-Walz G, Abraham D, Kissling W. Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo. A meta-analysis of randomized controlled trials. *Schizophr Res*. 1999; 35: 51–68.
21. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet*. 2009; 373: 31–41.
22. Möller HJ. State of the art of drug treatment of schizophrenia and the future position of the novel/atypical antipsychotics. *World J Biol Psychiat*. 2000b; 1: 204–214.
23. Möller HJ. Course and long-term treatment of schizophrenic psychoses. *Pharmacopsychiatry*. 2004; 37 (Suppl 2): 126–135.
24. Cheung HK. Schizophrenics fully remitted on neuroleptics for 3-5 years - to stop or continue drugs. *Brit J Psychiat*. 1981; 138: 490–494.
25. Cramer JA, Rosenheck R. Compliance with medication regimens for mental and physical disorders. *Psychiatr Serv*. 1998; 49: 196–201.
26. Oehl M, Hummer M, Fleischhacker WW. Compliance with antipsychotic treatment. *Acta Psychiatr Scand Suppl*. 2000; 102: 83–86.
27. Hogarty GE, Goldberg S, Schooler N, Ulrich R. Drug and sociotherapy in the aftercare of schizophrenic patients. II. Two-years relapse rates. *Arch Gen Psychiat*. 1974; 31: 603–608.
28. Leucht S, Busch R, Hamann J, Kissling W, Kane JM. Early-onset hypothesis of antipsychotic drug action: a hypothesis tested, confirmed and extended. *Biol Psychiat*. 2005; 57: 1543–1549.
29. Weiden PJ, Olfson M. Cost of relapse in schizophrenia. *Schizophrenia Bull*. 1995; 21: 419–429.
30. Bhanji NH, Chouinard G, Margolese HC. A review of compliance, depot intramuscular antipsychotics and the new long-acting injectable atypical antipsychotic risperidone in schizophrenia. *Eur Neuropsychopharmacol*. 2004; 14: 87–92.
31. Dolder CR, Lacro JP, Dunn LB, Jeste DV. Antipsychotic medication adherence: is there a difference between typical and atypical agents? *Am J Psychiat*. 2002; 159: 103–108.
32. Leucht S, Barnes T, Kissling W, Engel R, Kane JM. Relapse prevention in schizophrenia with new antipsychotics: a meta-analysis of randomized controlled trials. *Am J Psychiat*. 2003; 160: 1209–1222.
33. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *New Engl J Med*. 2005; 353: 1209–1223.

34. Kahn RS, Fleischhacker WW, Boter H, Davidson M, Vergouwe Y, Keet IP, Gheorghe MD, Rybakowski JK, Galderisi S, Libiger J et al. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. *Lancet*. 2008; 371: 1085–1097.
35. Adams CE, Fenton MK, Quraishi S, David AS. Systematic meta-review of depot antipsychotic drugs for people with schizophrenia. *Brit J Psychiat*. 2001; 179: 290–299.
36. Davis JM, Matalon L, Watanabe MD, Blake L, Metalon L. Depot antipsychotic drugs. Place in therapy. *Drugs*. 1994; 47: 741–773.
37. Kane JM. Dosing issues and depot medication in the maintenance treatment of schizophrenia. *Int Clin Psychopharm*. 1995; 10(Suppl 3): 65–71.
38. Möller HJ. Long-acting injectable risperidone for the treatment of schizophrenia: clinical perspectives. *Drugs*. 2007; 67: 1541–1566.
39. Akhras KS, Singh J, Gopal S, Schadrack J, Palumbo JM. Comparison of treatment completion rates for olanzapine pamoate and risperidone microspheres. *Int J Clin Pract*. 2009; 63: 962–963.
40. Citrome L. A review of aripiprazole in the treatment of patients with schizophrenia or bipolar I disorder. *Neuropsychiatr Dis Treat*. 2006; 2: 427–443.
41. Horne R. Long-term open label study of olanzapine pamoate: Efficacy and effect on weight. 161st Annual meeting of the APA, Arlington, USA. 2008.
42. Martinez G, Schreiner A. Risperidone long-acting injectable and olanzapine pamoate: review of short- and long-term data. Presented at the 9th WFSBP Congress Paris, France. 2009.
43. Canas F, Möller HJ. Long-acting atypical injectable antipsychotics in the treatment of schizophrenia: safety and tolerability review. *Expert Opin Drug Saf*. 2010; 9: 683–697.
44. Möller HJ. Risperidone: a review. *Expert Opin Pharmacother*. 2005; 6: 803–818.
45. Csernansky JG, Mahmoud R, Brenner R. A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. *New Engl J Med*. 2002; 346: 16–22.
46. Schooler N, Rabinowitz J, Davidson M, Emsley R, Harvey PD, Kopala L, McGorry PD, Van H, I, Eerdekens M, Swyzen W et al. Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. *Am J Psychiat*. 2005; 162: 947–953.
47. Kane JM, Eerdekens M, Lindenmayer JP, Keith SJ, Lesem M, Karcher K. Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. *Am J Psychiat*. 2003; 160: 1125–1132.
48. Chue P, Eerdekens M, Augustyns I, Lachaux B, Molcan P, Eriksson L, Pretorius H, David AS. Comparative efficacy and safety of long-acting risperidone and risperidone oral tablets. *Eur Neuropsychopharmacol*. 2005; 15: 111–117.
49. Fleischhacker WW, Eerdekens M, Karcher K, Remington G, Llorca PM, Chrzanowski W, Martin S, Gefvert O. Treatment of schizophrenia with long-acting injectable risperidone: a 12-month open-label trial of the first long-acting second-generation antipsychotic. *J Clin Psychiat*. 2003; 64: 1250–1257.
50. Kissling W, Heres S, Lloyd K, Sacchetti E, Bouhours P, Medori R, Llorca PM. Direct transition to long-acting risperidone-analysis of long-term efficacy. *J Psychopharmacol*. 2005; 19: 15–21.
51. Lasser RA, Bossie CA, Gharabawi GM, Kane JM. Remission in schizophrenia: Results from a 1-year study of long-acting risperidone injection. *Schizophr Res*. 2005b; 77: 215–227.
52. Patel MX, Young C, Samele C, Taylor DM, David AS. Prognostic indicators for early discontinuation of risperidone long-acting injection. *Int Clin Psychopharm*. 2004; 19: 233–239.
53. Rubio G, Martinez I, Ponce G, Jimenez-Arriero MA, Lopez-Munoz F, Alamo C. Long-acting injectable risperidone compared with zuclopenthixol in the treatment of schizophrenia with substance abuse comorbidity. *Can J Psychiat*. 2006; 51: 531–539.
54. Turner M, Eerdekens E, Jacko M, Eerdekens M. Long-acting injectable risperidone: safety and efficacy in stable patients switched from conventional depot antipsychotics. *Int Clin Psychopharm*. 2004; 19: 241–249.
55. Andreasen NC, Carpenter WT, Jr, Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. *Am J Psychiat*. 2005; 162: 441–449.
56. Emsley R, Medori R, Koen L, Oosthuizen PP, Niehaus DJ, Rabinowitz J. Long-acting injectable risperidone in the treatment of subjects with recent-onset psychosis: a preliminary study. *J Clin Psychopharmacol*. 2008a; 28: 210–213.
57. Emsley R, Oosthuizen P, Koen L, Niehaus DJ, Medori R, Rabinowitz J. Oral versus injectable antipsychotic treatment in early psychosis: post hoc comparison of two studies. *Clin Ther*. 2008b; 30: 2378–2386.
58. Kim B, Lee SH, Choi TK, Suh S, Kim YW, Lee E, Yook KH. Effectiveness of risperidone long-acting injection in first-episode schizophrenia: in naturalistic setting. *Prog Neuropsychopharmacol Biol Psychiat*. 2008; 32: 1231–1235.
59. Olivares JM, Rodriguez-Morales A, Diels J, Povey M, Jacobs A, Zhao Z, Lam A, Villalobos Vega JC, Cuellar JA, de Castro FJ et al. Long-term outcomes in patients with schizophrenia treated with risperidone long-acting injection or oral antipsychotics in Spain: results from the electronic Schizophrenia Treatment Adherence Registry (e-STAR). *Eur Psychiat*. 2009; 24: 287–296.
60. Schooler NR. Relapse and rehospitalization: comparing oral and depot antipsychotics. *J Clin Psychiat*. 2003; 64(Suppl 16): 14–7.

61. Gaebel W, Schreiner A, Bergmans P, de Arce R, Rouillon F, Cordes J, Eriksson L, Smeraldi E. Relapse prevention in schizophrenia and schizoaffective disorder with risperidone long-acting injectable vs quetiapine: results of a long-term, open-label, randomized clinical trial. *Neuropsychopharmacology*. 2010; 35: 2367–2377.
62. Möller HJ. Long-acting risperidone: focus on safety. *Clin Ther*. 2006; 28: 633–651.
63. 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 Neuropsychoph*. 2005a; 8: 427–438.
64. Gharabawi GM, Bossie CA, Zhu Y, Mao L, Lasser RA. An assessment of emergent tardive dyskinesia and existing dyskinesia in patients receiving long-acting, injectable risperidone: results from a long-term study. *Schizophr Res*. 2005; 77: 129–139.
65. Möller HJ, Llorca PM, Sacchetti E, Martin SD, Medori R, Parellada E. Efficacy and safety of direct transition to risperidone long-acting injectable in patients treated with various antipsychotic therapies. *Int Clin Psychopharm*. 2005; 20: 121–130.
66. Lindenmayer JP, Khan A, Eerdeken M, Van HI, Kushner S. Long-term safety and tolerability of long-acting injectable risperidone in patients with schizophrenia or schizoaffective disorder. *Eur Neuropsychopharmacol*. 2007; 17: 138–144.
67. Lasser RA, Bossie CA, Gharabawi GM, Turner M. Patients with schizophrenia previously stabilized on conventional depot antipsychotics experience significant clinical improvements following treatment with long-acting risperidone. *Eur Psychiat*. 2004; 19: 219–225.
68. Lindenmayer JP, Jarboe K, Bossie CA, Zhu Y, Mehnert A, Lasser R. Minimal injection site pain and high patient satisfaction during treatment with long-acting risperidone. *Int Clin Psychopharm*. 2005; 20: 213–221.
69. Thyssen A, Rusch S, Herben V, Quiroz J, Mannaert E. Risperidone long-acting injection: pharmacokinetics following administration in deltoid versus gluteal muscle in schizophrenic patients. *J Clin Pharmacol*. 2010; 50: 1011–1021.
70. Acosta FJ, Bosch E, Sarmiento G, Juanes N, Caballero-Hidalgo A, Mayans T. Evaluation of noncompliance in schizophrenia patients using electronic monitoring (MEMS) and its relationship to sociodemographic, clinical and psychopathological variables. *Schizophr Res*. 2009; 107: 213–217.
71. Rummel-Kluge C, Schuster T, Peters S, Kissling W. Partial compliance with antipsychotic medication is common in patients with schizophrenia. *Aust NZ J Psychiat*. 2008; 42: 382–388.
72. Walburn J, Gray R, Gournay K, Quraishi S, David AS. Systematic review of patient and nurse attitudes to depot antipsychotic medication. *Brit J Psychiat*. 2001; 179: 300–307.
73. Coldham EL, Addington J, Addington D. Medication adherence of individuals with a first episode of psychosis. *Acta Psychiatr Scand*. 2002; 106: 286–290.
74. Kamali M, Kelly BD, Clarke M, Browne S, Gervin M, Kinsella A, Lane A, Larkin C, O'Callaghan E. A prospective evaluation of adherence to medication in first episode schizophrenia. *Eur Psychiat*. 2006; 21: 29–33.
75. Llorca PM. Partial compliance in schizophrenia and the impact on patient outcomes. *Psychiatry Res*. 2008; 161: 235–247.
76. Heres S, Hamann J, Kissling W, Leucht S. Attitudes of psychiatrists toward antipsychotic depot medication. *J Clin Psychiat*. 2006; 67: 1948–1953.
77. Wobrock T, Sittinger H, Behrendt B, D'Amelio R, Falkai P, Caspari D. Comorbid substance abuse and neurocognitive function in recent-onset schizophrenia. *Eur Arch Psy Clin N*. 2006.
78. Heres S, Schmitz FS, Leucht S, Pajonk FG. The attitude of patients towards antipsychotic depot treatment. *Int Clin Psychopharm*. 2007; 22: 275–282.

PSYCHOTERAPIA

NR 4 (155) 2010

Index Copernicus 3,96
Liczba punktów MNiSW — 6

CONTENT

Jerzy W. Aleksandrowicz Irracjonalizm w psychoterapii.....	5
Małgorzata Talarczyk Ustawienia rodzin metodą Berta Hellingera.....	15
Paweł Bronowski, Maryla Sawicka Specjalistyczne usługi opiekuńcze jako ważny element środowiskowego leczenia osób chorych psychicznie.....	35
Katarzyna Hess-Wiktor, Małgorzata Opoczyńska Doświadczenie opieki nad bliskim dotkniętym chorobą Alzheimera.....	51
Renata Kleszcz-Szczyrba „Pomagać sobą” — rozważania na temat czynników niespecyficznych w psychoterapii związanych z osobą psychoterapeuty.....	63
Małgorzata Wolska Wskazania i przeciwwskazania do terapii małżeńskiej/terapii par.....	75

KRAKÓW — ZIMA 2010