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

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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.

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
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
Long-term pharmacotherapy of schizophrenic patients

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 labeling 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 retentation 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-naive 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 depot formulations, 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


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CONTENT

**Jerzy W. Aleksandrowicz**
Irracionalizm 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

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