Clinical overview

The case for long-acting antipsychotic agents in the post-CATIE era

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Objective: Long-acting antipsychotic agents were developed to promote treatment compliance in patients requiring maintenance treatment for schizophrenia.

Method: An analysis of the impact of non-compliance on treatment outcomes in schizophrenia and the advantages and disadvantages of long-acting antipsychotics.

Results: Partial or total non-compliance with oral antipsychotics remains widespread and is associated with significant increases in the risk of relapse, rehospitalization, progressive brain tissue loss and further functional deterioration. Long-acting agents have the potential to address issues of all-cause discontinuation and poor compliance. The development of the first long-acting atypical antipsychotic, which appears to be effective and well tolerated, should further improve the long-term management of schizophrenia.

Conclusion: Long-acting agents represent a valuable tool for the management of schizophrenia and merit wider use, especially in light of emerging literature regarding the neuroprotective advantages of atypical antipsychotics over conventional agents in terms of regenerating brain tissue during maintenance therapy.

Clinical recommendations

- Updating psychiatrists’ knowledge about the high discontinuation rates observed with oral antipsychotics may lead to more positive attitudes towards a greater reliance on long-acting formulations.
- Clearly communicated advantages of long-acting agents, such as lower neurological adverse effects and possibly enhanced neurotropic factors and neurogenesis may contribute to their broader acceptance.
- Additional studies are required to further substantiate the positive impact of long-acting risperidone on health-related quality of life and functioning.

Additional comments

- There are few published data on psychiatrists’ and patients’ attitudes to long-acting medications.
- In the more recent literature there is a paucity of data on long-acting conventional antipsychotic agents.
- The clinical and neurobiological effects of uninterrupted, prolonged medication compliance are required since, as demonstrated by the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, few patients remain on oral atypical agents to reap long-term benefits such as remission and possible neuroregeneration.
Introduction

Long-acting antipsychotic agents were developed in the 1960s as a novel method of drug delivery aimed at enhancing treatment compliance in patients with schizophrenia (thereby reducing the risk of rehospitalization and subsequent ‘revolving door’ in-patients), as well as simplifying the medication process (1, 2). It has been repeatedly demonstrated that poor and partial compliance with oral antipsychotic medication is high; more than 35% of patients begin to demonstrate compliance problems during their first 4–6 weeks of treatment, and only 25% are fully compliant within 2 years (3). This has been further supported by the results of the recent Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE), in which 74% of patients (n = 1493) who were assigned to the conventional antipsychotic agent perphenazine (up to 32 mg/day), or a range of oral atypical antipsychotics (olanzapine up to 30 mg/day, quetiapine up to 800 mg/day, risperidone up to 6.0 mg/day or ziprasidone up to 160 mg/day), discontinued medication within a few months (4). Non-compliance has been attributed to multiple factors including lack of insight, cognitive dysfunction, negative symptoms such as apathy, complicated treatment regimens, drug-related side-effects and lack of patient education (5–7).

Aims of the study

This article provides an overview of the impact of poor or partial compliance in schizophrenia and discusses the possibility of significantly reducing this problem by increasing the use of long-acting agents. Advantages and disadvantages of long-acting agents will be highlighted, along with a discussion of long-acting risperidone, the only atypical antipsychotic available in a long-acting injectable formulation at this time.

Material and methods

An analysis of published data was undertaken to examine: i) the impact of non-compliance on treatment outcomes in schizophrenia; ii) the advantages and disadvantages of long-acting antipsychotic agents and iii) current data on the first available long-acting atypical antipsychotic agent.

Results

Importance of consistent uninterrupted antipsychotic pharmacotherapy

Antipsychotic agents are the major class of drugs used in the treatment of schizophrenia. The atypical antipsychotics represent an improvement in both efficacy and tolerability over conventional agents (8–15). Emerging literature has also suggested that the atypical agents may have the potential to prevent or reverse the accelerated frontotemporal cortical gray matter decline commonly observed in schizophrenia patients (16–19). Indeed, several studies have demonstrated that the atypical agents may offer greater levels of neuroprotection compared with conventional agents in enhancing neurotropic growth factors and neurogenesis (20–22). However, despite these gains, optimal pharmacotherapy for schizophrenia remains problematic for a significant number of patients. Besides the emergence of metabolic adverse effects such as weight gain, hyperglycemia and hyperlipidemia with the newer agents (23–25), reliable and long-term disease control have often been limited by patients’ total or partial compliance with therapy (26).

In the case of schizophrenia, non-compliance has been shown to be highly correlated with inconsistent symptom control, relapse and rehospitalization, which in turn can lead to progressive brain tissue loss, family discord, danger to self and others and loss of autonomy, education or employment possibilities. Results from a randomized study that compared outcome measures of ‘highly compliant’ patients (medication possession ration: MPR of ≥70) vs. ‘less compliant’ patients (MPR of <70) demonstrated that a 20% reduction in the degree of treatment compliance predicts a 3.1 point increase in total Positive and Negative Syndrome Scale (PANSS) scores (Fig. 1) (27). Likewise, a comprehensive review of five randomized studies (28) demonstrated that there was an almost two-
fold increase in the risk of relapse in patients who received intermittent treatment (Fig. 2) (29–34). Finally, data from a cohort study of over 4000 patients with schizophrenia receiving antipsychotic therapy demonstrated that a gap in medication possession of as little as 1–10 days in a 1-year period doubles the risk of hospitalization (35), while another study which examined consecutive admissions to an acute patient unit reported that 50% of hospitalizations were attributable to medication non-compliance (2).

Advantages of long-acting antipsychotic agents

Long-acting antipsychotic agents have several advantages over oral agents, the major one being assurance of uninterrupted medication access (Table 1). Long-acting antipsychotics are convenient for the patient and their family who no longer have the burden of remembering to take medication on a daily basis. In addition, patients may also prefer the consistency that scheduled treatment provides. Indeed, one study demonstrated that as many as 67% of patients preferred long-acting agents because it afforded them a degree of control over the timing of their treatment (36). A less well-recognized advantage of long-acting agents is the more frequent contact between patients and treatment teams. Schizophrenia patients often live alone and have limited contact with other people. The necessary regular visits to the treatment center provide the opportunity for more formal psychosocial support such as psychoeducation or social skills training. Moreover, from a clinician’s point of view, a critical advantage of long-acting antipsychotics is that if a patient does become non-compliant, the clinical team will know immediately and will be able to initiate efforts to deal effectively with the problem before symptoms re-appear (37).

Long-acting antipsychotic agents also have several pharmacological advantages over their oral (immediate-release) counterparts. Administration of a long-acting agent avoids the variability associated with absorption and first-pass metabolism, and usually results in a better correlation between the administered dose and the plasma levels achieved (38, 39). Furthermore, once steady-state is achieved, plasma levels remain relatively stable, avoiding the daily peaks and troughs that occur with oral agents (38, 39). Long-acting antipsychotics also facilitate the use of the lowest effective dose principle, thereby reducing the frequency of adverse events, including akathisia, dysphoria and antipsychotic-induced deficit syndrome, and enhancing patient’s quality of life (40, 41). The risk of medication overdose with oral antipsychotics is also significantly reduced with long-acting agents; this is of significant importance given that suicide is a relatively common cause of death in psychotic patients [10–20% lifetime risk in those with schizophrenia (42, 43), and that most suicide attempts are with medication overdose (44)]. Although long-acting agents are unable to prevent relapse completely, with a systematic meta-review demonstrating that there is an irreducible 20–25% of patients who relapse despite receiving long-acting agents (45), when all of the data from individual trials and meta-analyses are taken together, the findings are quite compelling, in favor of long-acting agents. Results from a meta-analysis of six double-blind studies in 520 outpatients reported relapse rates to be significantly reduced among patients treated with long-acting
conventional agents (30.0%) vs. oral conventional agents (47.1%) (1). Furthermore, an analysis of data from mirror image studies in 613 out-patients reported significant differences in the number of hospitalization days between those on oral conventional medications (75 292 days) vs. long-acting conventional agents (17 860 days) (1). In addition, results from a prospective cohort study of 2230 consecutive adults with schizophrenia or schizoaffective disorder reported that the use of long-acting perphenazine was associated with a substantially lower risk of rehospitalization or discontinuation (for any reason) of therapy than the majority of the 10 most commonly used oral antipsychotic agents. Such reductions in hospitalization translate into significant cost savings (46).

However, despite the attractiveness of this treatment option, long-acting agents remain underutilized; in many countries throughout the world fewer than 20% of patients with schizophrenia receive these medications. Interestingly, prescribing practices for long-acting antipsychotic agents also differ significantly between countries, with higher rates of prescribing in Denmark, Sweden and the UK, and lower rates in France and the USA (47). Indeed, anecdotal reports indicate that only 10–20% of antipsychotic treatment in the USA involves long-acting formulations compared with as much as 50% in the UK.

Disadvantages of long-acting antipsychotic agents

The main objective disadvantage of long-acting agents is the rare occurrence of unexpected severe side-effects, such as tardive dystonia, dyskinesia and neuroleptic malignant syndrome (48–53). In addition, there is a fear on the part of clinicians that if adverse effects do occur, they will be more difficult to manage because of the inability to rapidly discontinue the medication. However, a review of the literature undertaken by Glazer et al. (48), which analyzed published data on neuroleptic malignant syndrome, tardive dyskinesia and extrapyramidal symptoms (EPS), did not support the assumption that long-acting conventional agents are associated with a greater risk of major side-effects than oral agents (54). As such, the authors concluded that 'the obvious advantages of these agents with regard to the problems of non-compliance, refractoriness and prevention of relapse need not be lost because of unfounded fears' (54).

Another potential disadvantage of the long-acting esterified oil-based conventional agents is the occurrence of injection site pain (55). In some cases the injection site can become edematous and tender or pruritic with a palpable mass being present for up to 3 months (56). In particular, haloperidol, fluphenazine, zuclopenthixol, and flupenthixol injections are all associated with significant pain and discomfort to the patient (55). As such, many physicians remain cautious about prescribing a long-acting agent, wishing to save the patient from the fear and pain of injections and believing that injections are a psychological intrusion.

Finally, some physicians believe that patients have negative attitudes toward receiving continual injections, particularly with regard to feeling overly controlled and losing their independence and freedom by receiving continual injections (57–59). However, the perceived loss of control is often more imagined than real and there are many other areas of everyday life where patients have ample opportunity to become autonomous without risking psychotic relapse. Furthermore, results from a systematic review of patient preference reported that in five of the six studies analyzed, the majority of patients preferred to receive their medication via a long-acting formulation than in tablet form (60). In reality, it is often the practitioners who have their own biases, resistances and negative thoughts about long-acting agents. Indeed, this was confirmed by the results of a recent cross-sectional postal survey of psychiatrists, which demonstrated that a substantial minority believed long-acting agents to be old fashioned (40%), stigmatizing (48%) and less acceptable to patients (69%) and relatives (66%). Some physicians may also associate long-acting agents with ‘non-compliant’ or ‘bad’ patients and, therefore, be reluctant to prescribe them (61).

The development of the first long-acting atypical antipsychotic agent

Risperidone is the first atypical antipsychotic to become available in long-term injectable form. Controlled trials demonstrate its efficacy, safety and tolerability (64, 65). Long-acting risperidone is unique among currently available long-acting antipsychotics because it is an aqueous suspension containing risperidone in a biodegradable matrix of glycolic acid–lactate polymer. In contrast with oil-based solutions, the aqueous nature of long-acting risperidone is associated with minimal pain, induration and inflammation at the injection site (62). The pharmacokinetic profile of long-acting risperidone exhibits less peak-trough variability (56–71% vs. 118–129% for oral risperidone), and 25–32% lower peak plasma concentrations than oral risperidone, due to the delayed release of active agent from the vehicle microspheres (63). These factors have been associated with both a
clinical improvement in symptom severity and a decrease in EPS vs. oral risperidone (33, 39).

Controlled clinical trials of long-acting risperidone

The clinical benefits of long-acting risperidone, vs. placebo and in the long term, have been explored in two large clinical trials, in which long-acting risperidone was administered at doses of 25, 50 and 75 mg every 2 weeks (64, 65). In a 12-week, randomized, controlled trial by Kane et al. (64), long-acting risperidone was associated with significantly greater improvements in PANSS total and factor (positive and negative symptoms) scores at endpoint compared with placebo ($P < 0.01$) (64). Statistically significant improvements in total PANSS scores ($P < 0.01$), positive symptoms ($P < 0.01$) and negative symptoms ($P < 0.001$) were also seen in the international, 1-year, open-label trial conducted by Fleischhacker et al. (65) in patients with schizophrenia who were switched to long-acting risperidone from oral or long-acting conventional or oral atypical antipsychotics. In the study by Kane et al. (64) similar proportions of patients in the placebo and long-acting risperidone groups (80–83%) reported adverse events, while long-acting risperidone was also well tolerated in the long-term trial by Fleischhacker et al. (65), with 65% of patients completing the trial. A number of studies have also demonstrated that patients can be switched from other oral and long-acting antipsychotic agents with minimal transition complications (66–68). In addition, long-acting risperidone has been shown to reduce episodes of hospitalization, an indicator of reduced relapse (69). Finally, preliminary data have demonstrated improvements in health-related quality of life and social functioning following treatment with long-acting risperidone (70, 71).

Of particular note, neither of the studies by Kane et al. (64) or Fleischhacker et al. (65) demonstrated significant differences in clinical outcomes for doses ranging from 25 mg/2 weeks or 75 mg/2 weeks, thereby suggesting that the optimal dose of long-acting risperidone may be less well established than that of oral risperidone (72). Furthermore, the observation that the lowest dose of long-acting risperidone gives rise to mean active moiety plasma levels of only 32.9 nmol/l, has lead to some debate as to whether a dose of 25 mg/2 weeks is truly effective in clinical practice (73).

Despite its proven efficacy in schizophrenia, many physicians continue to manifest a reluctance to adopt long-acting risperidone for its association with several ‘obstacles’. These primarily relate to the fact that some physicians feel long-acting risperidone is too complicated and time consuming to obtain, involving much paperwork, and is cumbersome to store and administer (74). However, although obtaining long-acting risperidone can take considerable personal time and effort, which can be a daunting task for those practitioners who are not surrounded by a team of nurses and administrative staff, it has become easier over time, and after the initial startup, paperwork is minimal (74). Long-acting formulations of other antipsychotics such as olanzapine and aripiprazole are also currently in development, but no data are as yet available.

Cost-effectiveness of long-acting risperidone

A number of studies and pharmacoeconomic models have demonstrated that long-acting risperidone decreases direct healthcare costs largely by reducing the rates of relapse and hospitalization (69, 75–79). Indeed, results from a 1-year international, open-label trial of long-acting risperidone in in-patients and out-patients with stable schizophrenia or schizoaffective disorder reported that the number of patients requiring hospitalization decreased continuously and significantly from 37% in the 3 months before treatment to 12% during the last 3 months of treatment (69). Of note, preliminary data from a Swedish multicenter study in 92 patients have demonstrated that for patients treated with long-acting risperidone, the total number of hospitalizations was reduced by 38% ($P = 0.0004$) compared with the same observational period when treated with their previous antipsychotic therapy (80). Using an empirical economic model, based on Swedish costs, the mean annual cost savings were estimated to be US$3600–6900 per patient following a switch to long-acting risperidone within the recommended dose range (80). However, in contrast to the various studies cited above, results from a recent study indicated that switching to long-acting risperidone was associated with a continuation of the trend for increased bed-stay and use of healthcare resources. In fact, the mean number of days per patient spent in hospital increased from 31 in the 3 years before initiation with long-acting risperidone to 141 following 1-year treatment with long-acting risperidone (81). Direct healthcare costs also rose accordingly. As such, further studies are required to clarify the cost-effectiveness of long-acting risperidone, and to determine the optimal dose and adjunctive psychosocial therapy required to achieve pharmacoeconomic advantages.

Long-acting risperidone costs about twice a comparable dose of oral risperidone, and that is
due in part to the cost of the prepackaged kit of vials, syringes, needles, and related items that come with each dose of injectable long-acting risperidone. However, the hidden cost of unused and wasted oral medication because of poor compliance is circumvented with full adherence to injectable medication.

**Discussion**

The introduction of long-acting antipsychotic agents was a major advance in the maintenance treatment of chronic schizophrenia. However, their use has declined in recent years, perhaps owing to the introduction of the oral atypical antipsychotic agents. Although long-acting agents have several advantages over oral medication, including improved treatment compliance and consistent drug delivery, an unjustified stigma in some, but not all countries, remains attached to their use which has been reinforced by required visits to specialized clinics at regular intervals. To address this, the advantages of long-acting agents, such as reduced relapse rates, improved tolerability and enhanced patient quality of life, should be clearly communicated to ensure wider future acceptance of these drugs by psychiatrists, patients and payers.

Parenteral and uninterrupted administration of long-acting risperidone should reduce hospitalization and the overall cost of care in a manner similar to that demonstrated by both the long-acting conventional agents and the atypical agents. However, long-term trials, which specifically address functional outcomes and relapse rates, as well as the development of emergent adverse outcomes, are required to further characterize the full impact of long-acting risperidone on the course of the illness and on treatment outcomes in schizophrenia and other recurrent psychoses including bipolar disorder.

In summary, long-acting antipsychotic agents that ensure continuous drug delivery and the provision of appropriate psychosocial therapy have the potential to address issues of all-cause discontinuation and poor compliance. Furthermore, it has been reported that some patients prefer long-acting formulations, thereby suggesting that physicians should more often recommend and prescribe a long-acting agent when antipsychotic maintenance therapy is indicated (58).

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The case for long-acting therapy


