Early Clinical Experience With Risperidone Long-Acting Injection: A Prospective, 6-Month Follow-Up of 100 Patients

David M. Taylor, Ph.D.; Corina L. Young, M.R.Pharm.S.; Shubhra Mace, M.R.Pharm.S.; and Maxine X. Patel, M.R.C.Psych.

Background: The use of risperidone long-acting injection (RLAI) is reasonably well supported by controlled studies. Little is known about treatment outcomes in patients receiving RLAI in clinical practice.

Method: All prescribers in the South London and Maudsley Trust, London, United Kingdom, were informed that RLAI could be ordered for suitable patients with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder: those known to be noncompliant with oral atypical antipsychotics and those intolerant of the adverse effects of conventional depot antipsychotics. Prescribers provided treatment and clinical progress data at the time of each prescription. Data collected included reason for prescribing RLAI, Clinical Global Impressions scale (CGI) score, inpatient or outpatient status, and details of all medications prescribed. All treatment discontinuations were investigated. The study was conducted from August 2002 to August 2003.

Results: Outcome could be determined for 100 subjects. Seventy-nine subjects (79%) were hospitalized when RLAI was initially prescribed. Mean duration of stay before RLAI initiation was 97 days (range, 0–1492 days). Most subjects were switched to RLAI from oral atypical (58%) or conventional depot (28%) antipsychotics. The main reason given for prescribing RLAI was poor patient acceptability of previous treatments (79%). Overall, 51% of the subjects discontinued RLAI. The main reason for discontinuation was lack of effect (24 subjects). No patient-related factor predicted outcome. CGI scores improved from a mean of 4.7 to 3.6 over the study period ($p < .001$). Overall, 61 subjects (61%) showed an improvement in CGI scores between baseline and endpoint. Antipsychotic coprescriptions were reduced from 71% of subjects to 8%. In completers, 23 (61%) of 38 subjects beginning RLAI as inpatients were discharged. The modal dose of RLAI was 25 mg every 2 weeks.

Conclusion: RLAI was moderately effective in clinical practice as judged by attrition from treatment. CGI score changes and discharge rates also suggest moderate effectiveness. RLAI was well tolerated. Antipsychotic coprescription was infrequent.

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Received Sept. 3, 2003; accepted Dec. 30, 2003. From the Pharmacy Department, Maudsley Hospital (Dr. Taylor, Ms. Young, and Ms. Mace), and Health Services Research, Institute of Psychiatry, DeCrespigny Park (Dr. Patel), London, United Kingdom.

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Corresponding author and reprints: David M. Taylor, Ph.D., Pharmacy Department, Maudsley Hospital, London SE5 8AZ, UK (e-mail: david.taylor@slam.nhs.uk).

Oral risperidone is an effective and well-tolerated atypical antipsychotic[1] that has been in widespread clinical use for more than 10 years. In 2002, a long-acting injectable form of risperidone was marketed in the United Kingdom and many other countries. This formulation consists of risperidone copolymer complex, which slowly hydrolyzes to release risperidone, allowing administration every 2 weeks.

Risperidone long-acting injection (RLAI) has been shown to be therapeutically equivalent to oral risperidone[2] and superior to placebo.[3] Uncontrolled data also show promising results.[4,5] Nonetheless, little is known about the utility of RLAI in everyday clinical practice. We undertook a prospective, naturalistic evaluation of RLAI in an urban clinical setting.

METHOD

RLAI was approved for use in the South London and Maudsley Trust in August 2002. All prescribers were informed that RLAI could be ordered for suitable patients with a DSM-IV diagnosis of schizophrenia or schizo-

Table 1. Antipsychotic Prescription Before Switching to Risperidone Long-Acting Injection (N = 100)

Antipsychotic Prescribed	N	%
Oral (non-clozapine) atypical	58	58
Conventional depot injection	28	28
Clozapine	4	4
Oral conventional	3	3
No prescription	7	7

Table 2. Reasons for Prescribing Risperidone Long-Acting Injection (N = 100)

Prescriber Reason	N	%
Poor patient acceptance (previous adverse effects or poor compliance)	79	79
Poor efficacy (previous poor response or relapse despite compliance)	10	10
No reason given (unknown)	11	11

affective disorder: those known to be noncompliant with oral atypical antipsychotics and those intolerant of the adverse effects of conventional depot antipsychotics. Trust pharmacies were instructed to dispense RLAI only on receipt of a valid prescription and an evaluation form completed in full by the prescriber and signed and dated by the prescriber. All prescription forms were photocopied, attached to the evaluation form, and filed.

The initial evaluation form included details about the patient, reason for prescribing RLAI, dose of RLAI prescribed, all concurrent drug treatment, and the clinician's rating of the patient's condition on the Clinical Global Impressions scale (CGI).[6] Further evaluation forms were completed for each injection prescribed (that is, every 2 weeks) for every patient for 6 months or until treatment was discontinued. All treatment discontinuations were investigated (by contacting the prescriber or by reference to case notes) and reasons for discontinuation recorded. Antipsychotic drugs prescribed immediately after discontinuation were also recorded (information from prescriber or case notes). Patient case notes were examined to determine antipsychotic prescription immediately before prescribing RLAI. The hospital computer record system was used to determine duration of hospital stay before initiation of RLAI. Statistical tests were performed using SPSS for Windows, version 10 (SPSS, Inc.; Chicago, Ill.). The study was conducted from August 2002 to August 2003.

RESULTS

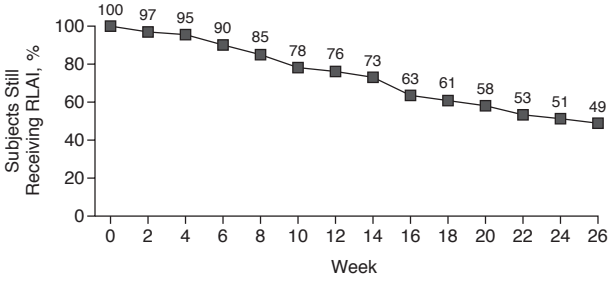
Subjects

We reviewed all patients starting RLAI in strict chronological order and analyzed the first 100 patients for whom the outcome could be determined. In total, 115 patients were reviewed and data for 15 patients discarded (12 were transferred to another area during the study period, and 3 were lost to follow-up). All 15 were still receiving RLAI when monitoring stopped, as far as could be ascertained. Mean follow-up in these 15 subjects was 14.5 weeks (range, 2–20 weeks).

Table 3. Antipsychotics Coprescribed During Initiation of Risperidone Long-Acting Injection (RLAI) (N = 100)

Antipsychotic	N	%
Risperidone	37	37
Olanzapine	10	10
Quetiapine	4	4
Clozapine	4	4
Amisulpride	2	2
Chlorpromazine	1	1
Conventional depot	13	13
No coprescription (conventional depot given immediately before RLAI)	15	15
No coprescription (no prior depot)	14	14

Figure 1. Attrition: Percentage of Subjects Still Receiving Risperidone Long-Acting Injection (RLAI) Versus Time (N = 100)



The remaining 100 patients formed the data set for analysis in this study. Data were analyzed on both an observed case basis (all data collected were used to calculate averages at specific time points) and only for those who completed 6 months of treatment with RLAI (completers) (disregarding all data from those who stopped receiving RLAI before week 26). Mean age of subjects was 42.9 years (SD = 13.7; range, 20–80 years). Sixty-one subjects were male.

Missing Data

Evaluations were not received for 36 time points (3.8%) of a total of 957 expected for the subject group (N = 100), taking into account duration of treatment for each subject. In each case, data were inserted by carrying forward the last observation.

Prescriptions

Tables 1 through 3 show other antipsychotic medications prescribed either before or during RLAI treatment and the reasons for prescribing RLAI.

Discontinuation From RLAI

Fifty-one subjects (51%) discontinued RLAI within 6 months. Numbers of subjects still receiving RLAI at all time points are shown in Figure 1. The details of why

Table 4. Risperidone Long-Acting Injection (RLAI) Discontinuation Details

Reason for Discontinuation	Details	Drugs Prescribed After Discontinuation
Ineffective (N = 24) (47% of those discontinuing)	Considered ineffective by prescriber (13) Considered ineffective by prescriber and prior history of treatment resistance (9) Relapsed (2)	Clozapine (10) Zuclopenthixol decanoate (4) Flupenthixol decanoate (4) Olanzapine (3) Haloperidol decanoate (1) Risperidone oral (1) Amisulpride (1)
Refused (N = 18) (35%)	Agreed to take oral medication (9) Refused all treatment (5) Did not attend for injection (3) Preferred typical depot (1)	Risperidone oral (8) No treatment (7)[a] Flupenthixol decanoate (1) Zuclopenthixol decanoate (1) Amisulpride (1)
Not tolerated (N = 9) (18%)	Pain at injection site (2) Dystonia (1) Weight gain (1) Sexual dysfunction (1) Mania (1) Edema (1) Eczema (1) Urinary incontinence (1)	Zuclopenthixol decanoate (2) Flupenthixol decanoate (2) Risperidone oral (1) Olanzapine (1) Quetiapine (1) Clozapine (1) No treatment (1)

[a]Two patients restarted RLAI treatment after 6-month assessment period.

Table 5. Risperidone Long-Acting Injection Discontinuations: Switching Summary (N = 51)

Drug	N	%
Conventional depot	15	29
Clozapine	11	22
Oral risperidone	10	20
Other atypical	7	14
No drug treatment	8	16

Table 6. Antipsychotic Treatment Before Initiation of Risperidone Long-Acting Injection (RLAI)

	Completed 6 mo RLAI (N = 49)		Discontinued RLAI (N = 51)	
Prior Antipsychotic Prescription	N	%[a]	N	%[a]
Oral (non-clozapine) atypical	25	51	33	65
Conventional depot injection	18	37	10	20
Clozapine	2	4	2	4
Oral conventional	1	2	2	4
No prescription	3	6	4	8

[a]Percentages may not sum to 100% due to rounding.

Table 7. Outcome Associated With Reason for Prescribing Risperidone Long-Acting Injection

Reason for Prescribing	N	Completed (N = 49)	Discontinued (N = 51)
Poor patient acceptability (previous adverse effects or poor compliance)	79	39	40
Poor efficacy (previous poor response or relapse despite compliance)	10	5	5
No reason given (unknown)	11	5	6

subjects discontinued RLAI are given in Table 4. Table 5 is a summary of drugs patients were switched to after stopping RLAI.

Table 6 lists antipsychotics prescribed before initiation of RLAI for those who discontinued RLAI and for those who completed 6 months of treatment. There was no statistically significant difference between these 2 groups in regard to prior treatment with oral atypicals or conventional depot ($\chi^2 = 3.4$, df = 1, p = .06). Clozapine was equally represented in both outcome groups. The numbers of subjects receiving oral conventional or no antipsychotics were too small for statistical analysis using a χ^2 test with Yates correction, but each was similarly represented in each outcome group.

Table 7 describes outcomes associated with different reasons given for prescribing RLAI. There was no statistically significant difference between completers and discontinuers in regard to reason given for prescribing RLAI ($\chi^2 = 0.0014$, df = 1, p = .98).

Mean age of those who continued was 43.6 years (SD = 15.7) and 41.6 years (SD = 12.3) for those who discontinued. There was no statistically significant difference in age according to outcome (2-sided, unpaired Student t test, p = .47). Twenty-eight men (57%) and 21 women (43%) completed 6 months of treatment. There was no significant difference in outcome according to gender ($\chi^2 = 0.60$, df = 1, p = .56).

Effectiveness—CGI Scores

Mean CGI scores fell from 4.7 (SD = 1.39) to 3.6 (SD = 1.73) over the study period (observed cases and completers, p < .001; Wilcoxon signed rank test). Analysis of completers and by intention to treat showed a statistically significant reduction in CGI by week 2 compared with time 0 (p = .01, both groups; Wilcoxon signed rank test). Figures 2A and 2B show mean CGI score against time for completers (N = 49) and for observed cases (N = 100 at t = 0).

Figure 2. Mean Clinical Global Impressions Scale (CGI) Score Versus Time for Subjects Receiving Risperidone Long-Acting Injection

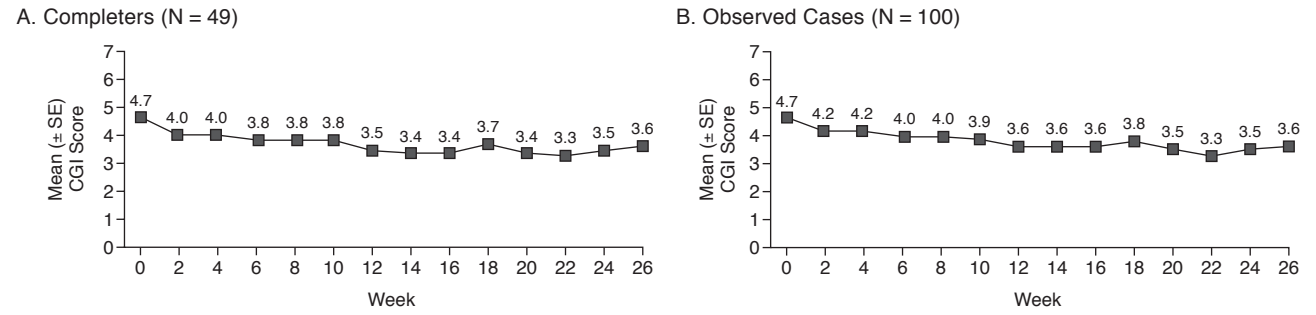
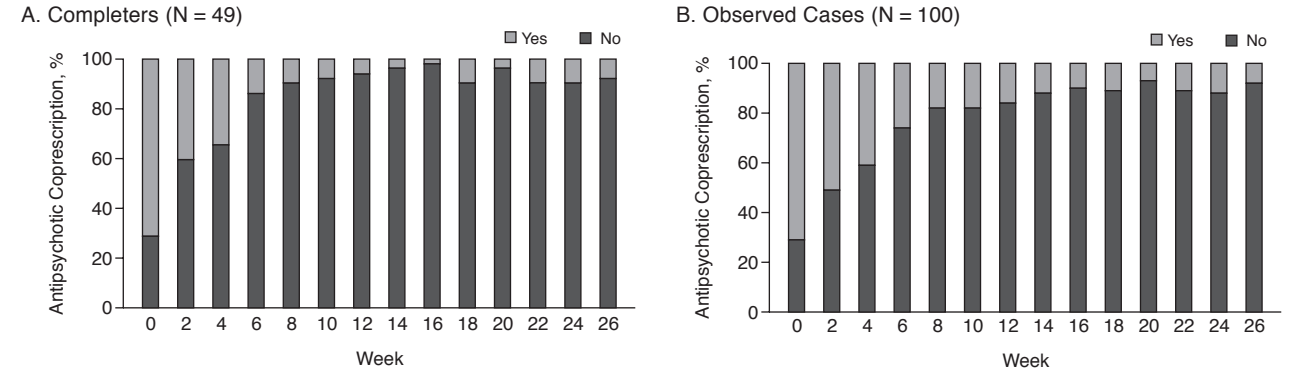


Figure 3. Proportion of Subjects Coprescribed Antipsychotics Versus Time



For each subject, the first and final CGI scores were compared. Final score was the last recorded score for those who discontinued RLAI and the score recorded at week 26 for those who continued for 6 months. Those subjects showing an increase in CGI score of at least 1 point were classified as "worsened," and those who showed a decrease of at least 1 point were classified as "improved." Those with the same CGI score at t = 0 and at endpoint were classified as "no change." Overall (N = 100), 61% of subjects improved, 17% saw no change, and 22% worsened. For those completing 6 months, 33 (67%) improved, 6 (12%) saw no change, and 10 (20%) worsened.

Antipsychotic Coprescription

The rate of antipsychotic coprescription fell from 71% to 8% over the 6-month study period (observed cases and completers). The change with time in proportion of subjects who were coprescribed antipsychotics with RLAI is shown in Figures 3A and 3B.

RLAI Dose

All but 1 subject (99%) began RLAI at a dose of 25 mg every 2 weeks, as suggested by the hospital protocol. One subject (1%) started at a dose of 37.5 mg every 2 weeks. The mean dose of RLAI rose from 25.1 mg (SD = 1.25) every 2 weeks to 35.7 mg (SD = 10.5) every 2 weeks (observed cases) and from 25.0 mg (SD = 0) every 2 weeks to 35.7 mg (SD = 10.5) every 2 weeks (completers). Mean dose change with time is shown in Figures 4A and 4B.

At study endpoint (determined as before, N = 100), 51% of subjects were receiving 25 mg every 2 weeks; 30%, 37.5 mg every 2 weeks; and 19%, 50 mg every 2 weeks. In those who completed 6 months of treatment with RLAI (N = 49), 21 (43%) were receiving 25 mg every 2 weeks at 6 months; 14 (29%), 37.5 mg every 2 weeks; and 14 (29%), 50 mg every 2 weeks. In those who discontinued RLAI (N = 51), 30 (59%) were receiving 25 mg every 2 weeks at endpoint; 16 (31%), 37.5 mg every 2 weeks; and 5 (10%), 50 mg every 2 weeks. The proportion of subjects prescribed each available dose of RLAI at each 2-week assessment is shown in Figures 5A and 5B.

Hospital Discharge

At the time of starting RLAI, 79% of all subjects (N = 100) were hospitalized and 21% were outpatients. Mean duration of hospitalization before starting RLAI was 97 days (range, 0–1492 days). At 6 months (N = 49), 16 subjects (33%) were hospitalized and 33 (67%) were outpatients. Change in inpatient status with time is shown in Figures 6A and 6B.

Figure 4. Mean Dose of Risperidone Long-Acting Injection (every 2 weeks) Versus Time

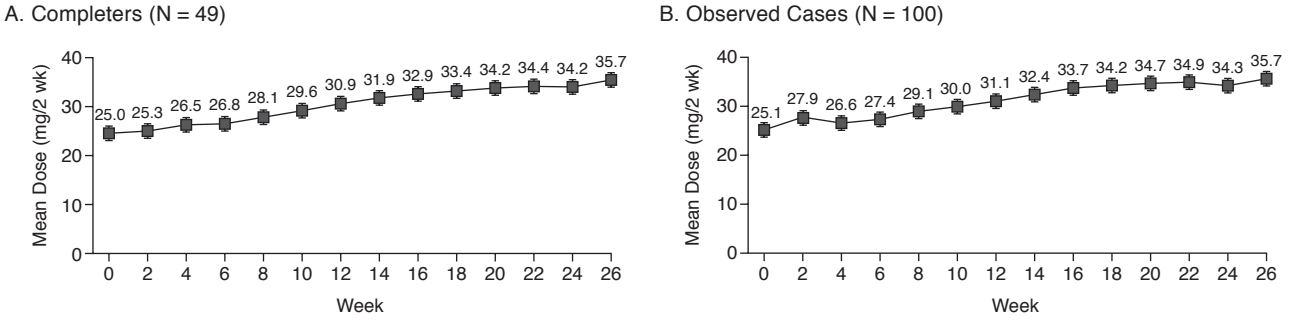


Figure 5. Percentage of Subjects Receiving Each Available Dose of Risperidone Long-Acting Injection (every 2 weeks) Versus Time

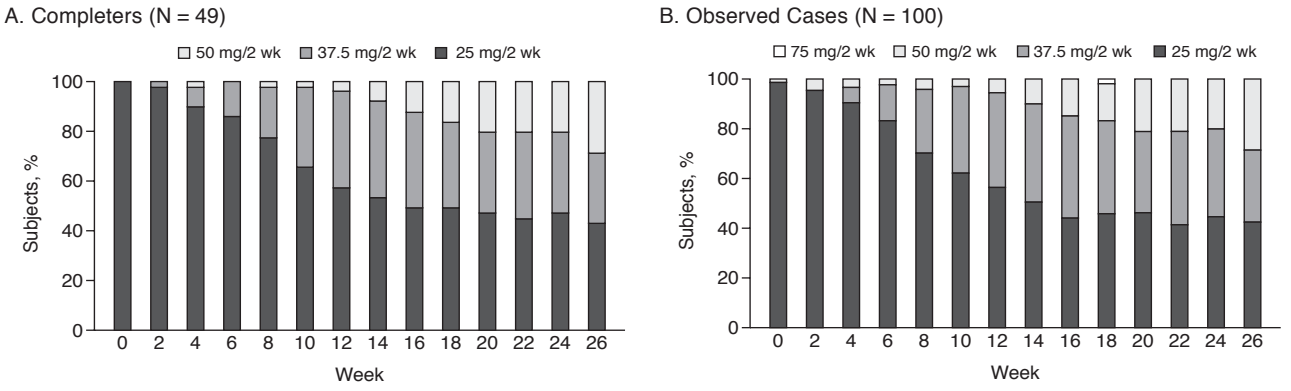
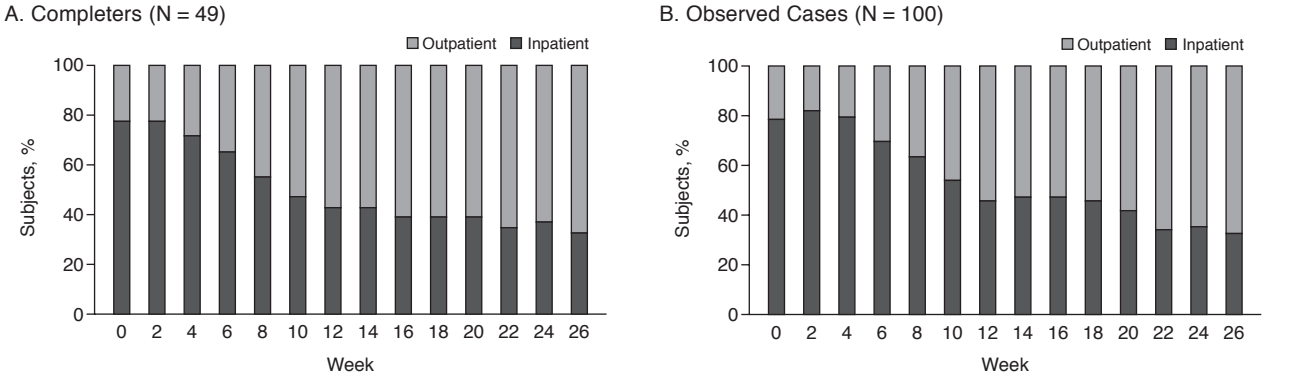


Figure 6. Percentage of Subjects' Inpatient/Outpatient Status Versus Time



Data were also analyzed for individual subjects, comparing inpatient versus outpatient status at initiation with status at endpoint and grouped as before. These data are summarized in Table 8.

Mean duration of hospital stay before RLAI initiation was 95 days for completers (N = 38, SD = 218; range, 1–1215 days) and 98 days for discontinuers (N = 41, SD = 255; range, 1–1492 days). There was no significant difference in duration of prior hospital stay between the 2 groups (unpaired, 2-tailed Student t test, p = .99).

DISCUSSION

Effectiveness

In naturalistic studies of antipsychotic treatment, perhaps the most robust indicator of successful outcome is

Table 8. Inpatient/Outpatient Status of Subjects at Endpoint

	All Subjects (N = 100)		Completers (N = 49)		Discontinuers (N = 51)	
Status	N	%	N	%	N	%
Remained inpatient	44	44	15	31	29	57
Discharged to outpatient	35[a]	35	23[b]	47	12[c]	24
Remained as outpatient	18	18	10	20	8	16
Readmitted	3	3	1	2	2	4

[a]35 (44%) of 79 inpatients discharged by endpoint.
[b]23 (61%) of 38 inpatients discharged by endpoint (6 months' treatment).
[c]12 (29%) of 41 inpatients discharged by endpoint.

continuation with treatment. In this study, almost half of those starting RLAI were still receiving the injection 6 months later, and of 51 patients who discontinued RLAI, 10 switched to oral risperidone. RLAI might thus be judged to be moderately effective in clinical practice.

Comparison with results of other antipsychotic studies may allow a more precise judgment of the clinical utility of RLAI. Attrition rates with oral atypical antipsychotics vary widely, but, as an example, 36% of patients allocated to olanzapine in clinical trials discontinued the drug by 6 weeks, and 83% discontinued the drug by 1 year.[7] Similar attrition rates have been reported with oral risperidone: 23% discontinuation in an 8-week randomized trial[8]; 47% discontinuation in a 3-month naturalistic study.[9] In studies of conventional depot antipsychotics, some reports suggest relatively low rates of attrition (e.g., 12.5% over 9 months[10]; 19% over 24 weeks[11]), whereas others report discontinuation rates similar to those seen in this study (e.g., 55% over 1 year[12]). The variation in attrition rates reported probably reflects differences in trial protocols as well as numerous other factors perhaps unrelated to drug efficacy or tolerability. One might expect, for example, relatively lower rates of attrition in randomized controlled trials in which consenting subjects are carefully selected and frequently monitored and evaluated. Attrition might be expected to be higher in naturalistic studies in which sometimes difficult-to-treat patients are less precisely selected and less frequently monitored. Indeed, in a 50-week controlled study of RLAI and placebo (N = 725),[5] only 35% of patients allocated to 1 of 3 doses of RLAI discontinued the drug over the study period. Taking into account all of these data, it can only be said that the attrition rate seen in this study is broadly in line with rates observed with other antipsychotics.

Outcome is inevitably affected by patients' level of illness. In this study, patients were mostly hospitalized, with a mean CGI score of 4.7 (between "moderately ill" and "markedly ill"). Duration of hospitalization before starting RLAI was unusually long, suggesting a cohort of patients with relapsed or chronic illness. The observed change in CGI score in the study was both statistically and clinically significant, suggesting a robust therapeutic effect for RLAI. Overall, 78 patients (78%) either improved or did not change by individual endpoint. For those completing 6 months of treatment (N = 49), 39 (80%) improved or did not change. These data largely support conclusions derived from attrition data: that RLAI was moderately effective in this group of patients. The main caveat here is the interpretation of CGI change given significant improvement at week 2—before risperidone had been released from the RLAI formulation. This improvement may reflect the action of coprescribed antipsychotics at the start of treatment with RLAI. In some cases, improvement may be associated with withdrawal of previously prescribed antipsychotics: essentially a drug-free period in which prior adverse effects abate.

Similar positive but cautious conclusions can be drawn from data relating to discharge and readmission. In those completing the study period, more than half of those who started RLAI as inpatients were discharged. Only 1 in 10 patients who started RLAI as outpatients was readmitted. This discharge rate, while suggesting worthwhile effectiveness, is substantially lower than that reported with oral risperidone (86% discharged within 120 days) in a similar U.K. clinical setting.[13] Possible reasons for this rate include the number of legally detained "forensic" patients in the study (10 subjects, 7 of those who completed the study), the pharmacokinetic profile of RLAI, and the level of treatment resistance in this cohort. Perhaps more importantly, the duration of hospital stay before RLAI suggests a difficult-to-treat study cohort among whom any discharge might be viewed as a significant therapeutic success. That such patients are afforded an important step in rehabilitation by the use of RLAI is noteworthy.

Subjects

Most subjects (58%) had been receiving oral atypical antipsychotics before being prescribed RLAI, with a substantial proportion (28%) receiving conventional depots. Prior treatment did not seem to predict outcome with RLAI, although discontinuation was numerically more often seen in those switched from oral atypicals and less often in those switched from conventional depots. According to prescribers of RLAI, most previously prescribed drugs (79%) had provided poor patient acceptability in some way. Of interest is that 10% of prescribers used RLAI in patients with poor prior response (despite our hospital protocol precluding such use), and 11% gave no reason (perhaps because of the hospital protocol restriction). The reason provided for prescribing RLAI did not predict the outcome.

The inclusion of treatment-resistant patients in this study cohort is very likely to have had a negative impact on outcome. However, the use of new products in difficult-to-treat patients is common practice, and so outcomes reported in this study are likely to be representative of normal clinical practice. As noted before, the duration of

prior hospitalization strongly suggests that this cohort had a poor prior response to treatment. Interestingly, duration of stay did not predict outcome as determined by continuation at 6 months.

Discontinuations

The main reason for stopping RLAI was lack of effect. Although reported treatment resistance did not predict outcome, an important proportion of those patients stopping had a prior history of treatment resistance (failure to respond to at least 2 antipsychotics). Many of these patients were ultimately prescribed clozapine, again suggesting that overall outcome was importantly affected by the prescribing of RLAI to resistant patients who might have been predicted not to respond[14] and for whom depot medication is not recommended.[15] Also of note is the low rate of withdrawals due to adverse effects (9% of subjects), suggesting reasonably good tolerability, and the number of subjects electing to switch from RLAI to oral risperidone, suggesting both good tolerability and effectiveness. The small but important proportion of patients refusing all treatment or not attending for injections is a reflection of normal clinical experience but may imply poor response or tolerability. Also of interest is that many of those stopping RLAI were switched to conventional depots, presumably reflecting some prescribers' greater confidence in the effectiveness and tolerability of these preparations. A small number of patients appeared to prefer conventional depot to RLAI. These are interesting observations given the debate over relative efficacy[16] and tolerability[17] of atypical and typical antipsychotics.

Antipsychotic Coprescription

On initiation of RLAI, the great majority of subjects were either coprescribed antipsychotics (71%) or were effectively still being treated with previously prescribed depot (a further 15%). Coprescribing is recommended for the first 3 to 4 weeks of treatment with RLAI because of delayed release of risperidone from the formulation. Changes in CGI scores during this time reflect the action of coprescribed antipsychotics (mainly risperidone and other atypicals) rather than RLAI itself. Of note is that 14% of patients did not receive antipsychotic treatment during RLAI initiation—these subjects were refusing oral treatment but reluctantly accepting RLAI injections.

The rate of coprescription declined markedly over time to less than 10% of subjects. This rate is substantially lower than that reported with oral risperidone prescribed in a similar setting.[13] Our hospital protocol precluded the coprescription of other antipsychotics with RLAI after the initiation period. Accordingly, all such prescriptions were challenged by pharmacy staff, and thus low rates of coprescription might have been expected. These low rates afford a clear picture of the effect of RLAI used as the sole antipsychotic in a naturalistic setting. That such low rates were observed, however, is perhaps most likely to be a result of the efficiency of protocol enforcement rather than any intrinsic effect of RLAI.

RLAI Dose

No trial has demonstrated that doses of RLAI above 25 mg every 2 weeks confer any additional benefit. Our protocol recommended that all subjects start at this dose regardless of previous treatment dosage. Average dose gradually rose during the study period but seems to have begun to level off by 6 months. Approximately half of those continuing RLAI were managed on 25 mg every 2 weeks. In those who discontinued, only 10% had been given a trial of the highest dose, 50 mg every 2 weeks. Clearly, more research is needed to establish the optimum dose of RLAI, especially since the cost effectiveness of RLAI is partly dependent on the dose, and therefore cost, of the injection.

Study Limitations

The main limitation of this study is the incomplete information available to establish the precise nature of the study cohort. For example, data collection did not include full psychiatric or drug histories for subjects. Moreover, patient details provided by prescribers of RLAI might be viewed with some suspicion, since prescribers may well have erroneously reported protocol-compliant reasons for prescribing RLAI in order to avoid a refusal to supply by the pharmacy. Another major limitation is the questionable reliability of the CGI scores provided by untrained observers whose judgment may well have been affected by expectations of RLAI treatment. Perhaps connected to this possible limitation is the observation that CGI scores reduced significantly by week 2, a time at which essentially no risperidone had been released from RLAI administered 2 weeks previously. These factors make interpretation of the results somewhat difficult.

Despite these shortfalls, this study usefully reports a cogent treatment outcome (continuation at 6 months) in what might be expected to be a typical clinical cohort of patients in a naturalistic setting. In addition, the clear trend in CGI mean scores coupled with low standard error values suggests some reliability for this measure in this study.

CONCLUSIONS

This preliminary investigation indicated that RLAI was moderately effective in this naturalistic study as judged by attrition from treatment, change in CGI score, and rate of discharge from hospital and taking into account the level of treatment resistance in the study cohort. The main reason for stopping RLAI was lack of effect, and many of those not responding were considered treatment resistant before starting RLAI. Very few subjects

discontinued RLAI because of adverse effects. Antipsychotic polypharmacy was rarely required in subjects stabilized on RLAI, and almost half of those completing 6 months of treatment received the minimum licensed dose of 25 mg every 2 weeks. Further research is required to establish which patients are most likely to respond to RLAI and to determine longer-term outcome with this depot antipsychotic preparation. While this study did not reveal clear predictors of response or success with RLAI, data arguably support the notion that RLAI is most effectively used in stable patients being switched from conventional depots.

Drug names: chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and Risperdal Consta).

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