Risperidone Long-Acting Injection: A Prospective 3-Year Analysis of Its Use in Clinical Practice

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Objective: To evaluate outcomes of clinical use of risperidone long-acting injection (RLAI) and determine factors predicting continuation with treatment.

Method: This prospective, 3-year follow-up of consecutive patients started on treatment with RLAI in normal clinical practice between August 2002 and September 2003 obtained demographic and clinical data from case notes, prescription charts, and hospital computer records. To determine predictors of continuation, a proportional hazards regression (Cox) model was constructed.

Results: The study included 211 evaluable patients. Over 3 years, 84% of subjects discontinued RLAI; 27.7% of these switched to oral risperidone. The Cox model showed that younger age ($p = .001$), longer duration of illness ($p = .001$), inpatient status at initiation ($p = .002$), and an RLAI dose of 25 mg/2 weeks ($p < .001$) predicted greater probability of discontinuation.

Conclusion: A small proportion of patients initiated on treatment with RLAI continued for 3 years. Outcome is likely to be improved by targeting RLAI treatment at specific patient groups and by using a dose of more than 25 mg/2 weeks.

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Risperidone long-acting injection (RLAI) has been shown to be an effective antipsychotic in controlled trials at doses between 25 mg and 75 mg every 2 weeks.[1] However, the recent Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study showed that favorable results in well-controlled efficacy studies might not predict positive outcomes in a more naturalistic environment.[2] In particular, all drugs in this study showed high discontinuation rates over the 18-month study period.

Naturalistic data also suggest very high dropout rates are associated with the use of depot injections, including RLAI.[3] Our own 6-month[4] and 1-year[5] data have also suggested a high discontinuation rate with RLAI, largely related to younger age and the use of lower maintenance doses of RLAI.[6] Other sources, too, have given rise to some doubt over the clinical utility of the 25-mg dose of RLAI in some patient populations.[7,8] We now report on 3-year data related to our research cohort.

METHOD

Risperidone long-acting injection was approved for use in South London and Maudsley National Health Service trust in August 2002. All patients consecutively initiated on treatment with RLAI between August 2002 and September 2003 were included in the study, which was approved under hospital audit governance regulations. Prescribers were advised that RLAI was available for patients with schizophrenia or schizoaffective disorder and who were known to be noncompliant with oral antipsychotics or were intolerant to conventional depot antipsychotic. A starting dose of 25 mg every 2 weeks was recommended for all patients.

Risperidone long-acting injection was dispensed by trust pharmacies upon submission of a valid prescription and an evaluation form. The form requested details about the patient (age, diagnosis), reason for prescribing, prior treatment, patient's current care status (inpatient or outpatient), dose prescribed, and all concurrent drug treatment.

Patient case notes and computerized records were scrutinized to confirm information provided by the prescribers. Case notes also provided patient details as

Table 1. Demographic and Clinical Characteristics of Patients Receiving Risperidone Long-Acting Injection (RLAI)

Parameter	Study Sample (N = 211)
Age at initiation, mean (SD), y	38.4 (12.3)
Age at initiation, range, y	18–79
Gender, N (%)	
Male	135 (64.0)
Female	76 (36.0)
Diagnosis, N (%)	
Schizophrenia[a]	172 (81.5)
Bipolar disorder	15 (7.1)
Other[b]	24 (11.4)
Years of psychiatric illness (N = 188), mean (SD)	11.2 (8.9)
Years of psychiatric illness (N = 188), range	0–45
Ethnicity, N (%)	
White	62 (29.4)
Black	120 (56.9)
Asian	13 (6.2)
Mixed race	13 (6.2)
Other	3 (1.4)
Bed status at initiation, N (%)	
Inpatient	144 (68.2)
Outpatient	67 (31.8)
Reason for starting RLAI, N (%)	
Prior poor compliance	122 (57.8)
Prior poor tolerability	47 (22.3)
Reasons unknown	27 (12.8)
Prior poor efficacy	15 (7.1)

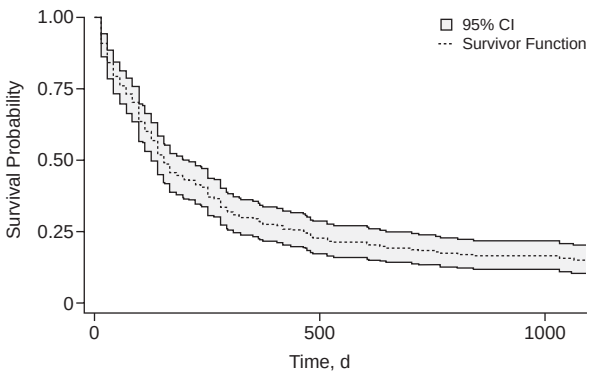
[a]Includes schizophrenia and schizoaffective disorder.
[b]Includes mood affective disorders, mental and behavioral disorder, psychotic symptoms with dementia, psychotic depression, personality disorder, pervasive developmental disorder, psychosis, acute and transient psychotic disorder, organic mental disorder, and persistent delusional disorder.

follows: age, gender, ethnicity, diagnosis, duration of diagnosed illness, status (inpatient or outpatient) when RLAI was first prescribed, history of previous clozapine therapy, antipsychotic and anticholinergic co-prescription during RLAI treatment, antipsychotic prescribed immediately before RLAI, and the antipsychotic switched to if RLAI was discontinued. All patients were followed up for 3 years after starting RLAI. Those who left the care of the trust during the study period were excluded. The highest dose of RLAI reached (termed simply "dose" for the purposes of this study) was obtained from computer records and prescription charts. Co-prescription of other antipsychotics was actively discouraged after initial titration of RLAI.

The main outcome of interest was continuation with RLAI treatment. In order to investigate the relationship between continuation with treatment and patient characteristics, a proportional hazards regression model was fitted (Cox model). Discontinuation of treatment was treated as the event of interest. Time on treatment was calculated as the time from starting RLAI to discontinuation of treatment or to 3 years after the first treatment date, whichever was sooner.

Poisson and negative binomial regression models were used to explore the relationship between patient characteristics and discontinuation. The negative binomial regression model allows for overdispersion in the observed data (i.e., if the observed variation is greater than that assumed by the model); not accounting for this variation will cause the standard errors to be biased downward; hence, variables are more likely to be statistically significant.

Figure 1. Kaplan-Meier Plot of Treatment Duration Showing Survival Function and 95% Confidence Interval for 211 Patients



All models were fitted by initially including all baseline and treatment characteristics listed in using a stepwise selection procedure (20% inclusion criteria). Interactions of variables were checked, and the fit of the models was then examined using residual analysis. The squared linear predictor was tested for significance to assess the model specification; residual analysis was performed to examine specific model assumptions and to determine the functional form of the continuous variables.

RESULTS

In total, 277 patients were initiated on treatment with RLAI during the study period. During the 3-year follow-up, 46 patients were transferred to care in another catchment area, 11 were lost to follow-up, and 9 died. The remaining 211 patients formed the data set for the analysis in this evaluation (Table 1). The main outcome was continuation with RLAI at 3 years. Overall, 34 patients (16%) completed 3 years of treatment and 177 (84%) discontinued. Median time to discontinuation was 154 days (95% CI = 126 to 210 days) (Figure 1).

Antipsychotics prescribed before initiation of RLAI, during its titration, and after its cessation are described in Table 2. Reasons for discontinuation of RLAI are given in Table 3. Adverse effects resulting in discontinuation are given in Table 4.

For discontinuers, dose of RLAI at cessation was 12.5 mg/2 weeks for 1 patient (0.6%), 25 mg/2 weeks for 82 (46.3%), 37.5 mg/2 weeks for 53 (29.9%), 50 mg/2 weeks for 39 (22.0%), and 75 mg/2 weeks for 2 (1.1%). In those

Table 2. Sequence of Antipsychotic Prescribing

Antipsychotic/ Group	Antipsychotic Before RLAI (N = 211), N (%)	Antipsychotic During RLAI Titration (N = 211), N (%)	Antipsychotic After RLAI (N = 177), N (%)
Risperidone oral	74 (35.1)	114 (54.0)	49 (27.7)
Oral atypical[a]	45 (21.3)	23 (10.9)	31 (17.5)
Depot typical	66 (31.3)	14 (6.6)	39 (22.0)
Oral typical	8 (3.8)	2 (0.9)	11 (6.2)
No antipsychotic	15 (7.1)	52 (24.6)	20 (11.3)
Clozapine	3 (1.4)	1 (0.5)	27 (15.3)

[a]Includes aripiprazole, amisulpride, olanzapine, and quetiapine.
Abbreviation: RLAI = risperidone long-acting injection.

Table 3. Reasons for RLAI Discontinuation (N = 177)

Reason	N (%)
Ineffective	64 (36.2)
Patient choice[a]	66 (37.3)
Adverse event	37 (20.9)
Other	10 (5.6)

[a]Includes subjects who refused to accept RLAI or actively defaulted on RLAI treatment.
Abbreviation: RLAI = risperidone long-acting injection.

Table 4. Adverse Effects Resulting in RLAI Discontinuation (N = 37)

Adverse Effect	N[a]
Acute movement disorder[b]	7
Sexual dysfunction	5
Pain at injection site	4
Akathisia/agitation	4
Sedation	4
Weight gain	3
Not stated in case notes	3
Peripheral edema	2
Numbness	1
Abscess at injection site	1
Hypersexuality	1
Rash	1
Eczema	1
Pain in legs	1
Urinary incontinence	1
Collapse following administration	1
Palpitations	1

[a]Some patients reported more than 1 adverse effect.
[b]Parkinsonism, N = 6; dystonia, N = 1.
Abbreviation: RLAI = risperidone long-acting injection.

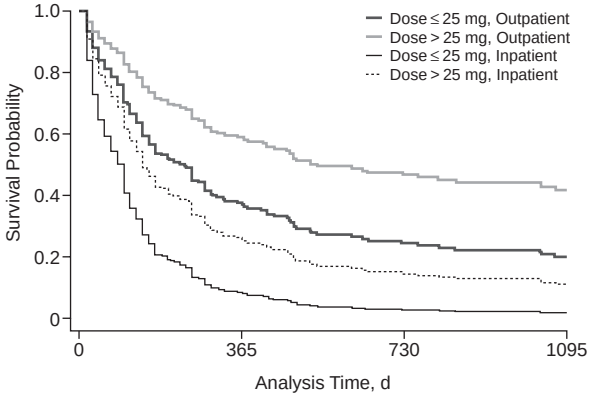
who continued RLAI for 3 years, dose at 3 years was 25 mg/2 weeks for 16 patients (47.1%), 37.5 mg/2 weeks for 9 (26.5%), and 50 mg/2 weeks for 9 (26.5%). Mean final dose was 34.7 mg/2 weeks in discontinuers and 34.9 mg/2 weeks in continuers (t test, p = .93). Highest dose reached was the same as cessation dose/3-year dose in each case, except for the 1 patient who received 12.5 mg/2 weeks.

For those ceasing RLAI because of ineffectiveness (N = 64), 18 patients discontinued having reached a dose of 25 mg/2 weeks (28.1%), 19 patients at 37.5 mg/2 weeks (29.7%), 25 patients at 50 mg/2 weeks (39.1%), and 2 patients at 75 mg/2 weeks (3.1%).

Table 5. Variables Associated With Discontinuing Treatment in the Cox Proportional Hazards Analysis

Variable	Hazard Ratio	95% CI	p Value
Age	0.97	0.95 to 0.99	.001
Dose (≤ 25 mg vs > 25 mg)	0.54	0.39 to 0.75	< .001
Duration of illness	1.06	1.03 to 1.10	.001
Inpatient/outpatient status at initiation	2.52	1.41 to 4.53	.002
Inpatient/outpatient status at initiation/duration of illness	0.95	0.91 to 0.99	.011

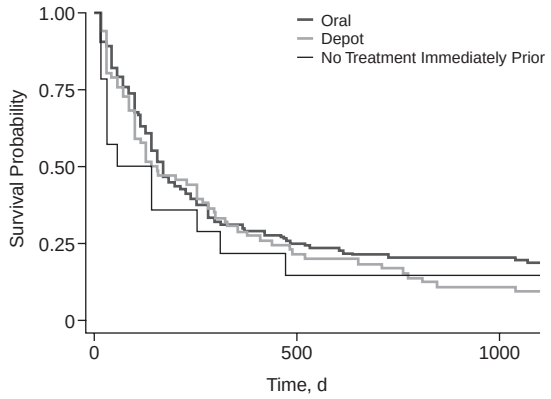
Figure 2. Predicted Survival Probabilities Using the Cox Proportional Hazards Model for Dose and Inpatient/ Outpatient Status at Start of Treatment, Assuming Mean Age and Duration of Illness



The Cox model fit was found to be reasonable, and 4 variables were found to be associated with discontinuing treatment. The estimated hazard ratios and 95% CIs can be seen in Table 5. The results of the model estimated that a 1-year increase in age was associated with a 3% decrease in hazard of discontinuing treatment (p = .001), and a dose of > 25 mg was associated with a 46% decrease in hazard of discontinuing treatment compared to a dose of ≤ 25 mg (p < .001) (Figure 2). A 1-year increase in duration of illness was associated with an estimated 6% increase in hazard of discontinuing treatment (p = .001). Being an inpatient at initiation of treatment was associated with an estimated 150% increase in hazard of discontinuing treatment compared to being an outpatient (p = .002). In addition, an interaction between inpatient/outpatient status at initiation and length of illness was found. Increased duration of illness was associated with an increased hazard of discontinuing treatment in outpatients, and an increased duration of illness was associated with a decreased hazard of discontinuing treatment in inpatients.

No other recorded patient, demographic, or clinical factor (gender, ethnicity, diagnosis, anticholinergic use, history of clozapine use, prior antipsychotic, use of oral

Figure 3. Predicted Survival Probabilities Using the Cox Proportional Hazards Model for Prior Antipsychotic Treatment, Assuming Mean Age and Duration of Illness



risperidone during titration, or reason for prescribing [$p > .2$ for all]) was statistically associated with discontinuation (see Figure 3 for effect of prior antipsychotic).

DISCUSSION

The main finding of this observational study was that 84% of patients discontinued RLAI within 3 years, although 27.7% of these switched, at least initially, to oral risperidone. Although only 7.1% of patients began RLAI because of poor prior efficacy, 36.2% discontinued RLAI because of ineffectiveness. Patient choice and insufficient effect accounted for more than 70% of discontinuations. Factors associated with a significantly greater likelihood of discontinuation were inpatient status on initiation, younger age, longer duration of illness, and the use of a dose of 25 mg/2 weeks.

Patient age and dose were previously found to predict continuation with RLAI at 6 months.[6] Indeed, younger age, inpatient status, and longer duration of illness might confidently be expected to portend poor outcome with any antipsychotic since each factor suggests more severe illness. In addition, plasma levels of risperidone and its active metabolite tend to be substantially higher in older patients.[9]

The issue of RLAI dose is complex and remains unresolved. Our study strongly associated doses above 25 mg/2 weeks with an increased likelihood of continuation. This observation is confounded by the fact that doses tend to increase as treatment persists; that is, continuation with treatment is likely to predict higher doses. Nonetheless, these higher doses presumably result from titration against clinical effect. Fixed-dose, randomized controlled trials strongly suggest that the 25-mg dose is at least as effective as higher doses.[10] Conversely, alongside findings related to our patient cohort, there is much to suggest that 25 mg/2 weeks is relatively less effective. For example, patients switched from 4 mg/day oral risperidone to 25 mg/2 weeks RLAI were found to show decreased plasma levels and an increased tendency to relapse.[8] Other observational studies have revealed that patients receiving 25 mg/2 weeks had largely subtherapeutic plasma levels.[11,12] Further studies suggest that dopamine D_2 receptor occupancy associated with 25 mg/2 weeks is probably insufficient to provide therapeutic effects.[13,14] That some patients do well on 25 mg/2 weeks is perhaps not in doubt (nearly half of those completing this study did so on this dose), but it is less clear as to whether or not it is as effective overall as higher doses. Also, it is notable that comedication with additional antipsychotics, although not reported in this study, is unlikely to be a confounding factor here: comedication is actively discouraged in our unit, and antipsychotic polypharmacy was seen in less than 10% of patients in this cohort at 6 months.[4]

Given the high discontinuation rate in this study, it is right to consider the nature of our patient cohort. Our trust treats both patients from our local area (a socially deprived region of South East London) and more difficult-to-treat cases from around the United Kingdom. In our study cohort, almost all patients were drawn from the local population and few had previously been exposed to clozapine (a proxy for confirmed treatment resistance). However, the observation that substantially more patients (15.3%) were switched to clozapine than from it (1.4%) does suggest important levels of treatment resistance in this cohort. An important limitation of this study is that treatment responsiveness was not formally assessed at baseline. Interestingly, prior clozapine use did not predict discontinuation in this study, although this factor did predict a reduced likelihood of clinical improvement at 6 months.[6] Reason for prescribing RLAI (including prior poor response) was not associated with continuation in this study.

Other factors possibly contributing to poor outcome include insufficient experience with using a new formulation and poor knowledge of its pharmacokinetic properties.[15] We know of no other 3-year follow-up data for RLAI, but shorter naturalistic studies have shown discontinuation rates ranging from 42% (1 year)[16] to 97.7% (180 days).[3] Against these findings, our results do not seem unusual.

RLAI appeared to be fairly well tolerated in this study—only just over 20% of patients discontinued because of adverse effects. The pattern of adverse effects observed is largely consistent with the expectation that risperidone causes both extrapyramidal symptoms and symptoms relating to hyperprolactinemia, albeit in a minority of patients. Some of the adverse effects reported as being the cause of RLAI cessation (e.g., eczema, leg pain) seem unlikely to be related to the use of RLAI. It is notable that 5 patients ceased treatment with RLAI because

of injection-site problems (pain, abscess). The proportion of patients opting to switch to oral risperidone also suggests some negative perceptions of RLAI as a formulation, as opposed to the drug itself.

Limitations to this study include the aforementioned absence of formal assessment of treatment responsiveness, the lack of long-term assessment of clinical response (reported only at 6 months[6]), and the somewhat limited number of patient and demographic factors analyzed (for example, the influence of prior antipsychotic dose and number of previous antipsychotics was not evaluated). Strengths of the study include the near completeness of follow-up of the original cohort, the efficiency of data capture (we had no missing data points for the study cohort), and the sophistication of the statistical analysis.

The findings of this study have some value in optimizing the use of RLAI. The use of RLAI at doses above 25 mg/2 weeks in older outpatients is likely to be successful, whereas its use in lower doses in younger inpatients is very likely to be unsuccessful (see Figure 2). RLAI should not be used in those who are treatment resistant given the absence of studies demonstrating its utility and the number of treatment failures in the present study. Patient selection clearly has a major influence on outcome. Targeting the use of RLAI has the potential greatly to enhance the cost-effectiveness of this valuable product—RLAI should be quickly titrated to an effective dose in patients known to be responsive to antipsychotic treatment.

Drug names: aripiprazole (Abilify), clozapine (FazaClo, Clozaril, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others).

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