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Risperidone long-acting injection: the first 50 patients

AIMS AND METHOD

Risperidone long-acting injection (RLAI) is the first atypical antipsychotic drug to be available in a 'depot' formulation. The evidence base underpinning its use is small. We sought to evaluate its early use in clinical practice by a naturalistic follow-up study of the first 50 patients to be prescribed RLAI in one National Health Service Trust.

RESULTS

At 6 months, 54% of patients had achieved at least minimal improvement, 4% were unchanged, 24% failed to comply, and 18% fared poorly and were switched to alternative antipsychotics. The attrition rate at 6 months was 42%. Supplementation with oral antipsychotics was often required for longer than 3 weeks. Only half of those who had a good clinical outcome at 6 months had achieved this by 3 months.

CLINICAL IMPLICATIONS

Some patients responded well to RLAI, but the overall attrition rate was high. Although RLAI provides additional choice in the range of treatments available for people with schizophrenia, we have much to learn about how to optimise its use in practice.

Atypical antipsychotic drugs are associated with fewer neurological side-effects than the older conventional drugs (Geddes *et al*, 2000) and patients generally find them more tolerable (National Schizophrenia Fellowship, 2001). The National Institute for Clinical Excellence (2002) recommends that atypicals should be considered in the choice of treatment for all patients experiencing a first episode and for patients suffering unacceptable side-effects with conventional drugs. This guidance covers schizophrenia only. Non-complicance with medication is a major cause of relapse and rehospitalisation in patients with schizophrenia and depot antipsychotics are still widely used in the UK to overcome this (Adams *et al*, 2001). Risperidone long-acting injection (RLAI) is the first atypical antipsychotic to be available in depot form and as such widens the choice of treatments for patients with psychotic illnesses. The aims of this study were to describe the efficacy and attrition rate from treatment with RLAI in one mental health trust.

Method

The following data were collected prospectively for the first 50 patients prescribed RLAI in Oxleas National Health Service (NHS) Trust: patient's name, service directorate, reason for prescribing, dosage and clinical outcome after 3 months, and dosage and clinical outcome after 6 months. Clinical outcome was rated by the prescriber using the Clinical Global Impression (change) scale (Guy, 1976). Using this scale, patients were rated as being very much improved, much improved, minimally improved or no change. Consultants were asked to rate response in light of the original reason for prescribing RLAI. For example, patients who previously had stable psychotic symptoms but were switched to RLAI because of intolerable extrapyramidal side-effects would be rated as very much improved if their psychotic symptoms did not change but their side-effects diminished substantially.

As the study was naturalistic, patients whose mental state deteriorated were switched to alternative treatments at the prescribers' discretion. Such patients were grouped together and rated as 'treatment failures', indicating that the prescriber had taken the decision to change treatment. Patients who actively refused medication or failed to keep appointments so that administration was too erratic to be effective were rated as 'refused'.

Results

Why was RLAI prescribed?

Forty-two patients had a history of non-compliance with oral medication and had experienced unacceptable extrapyramidal side-effects with conventional depot medication. Two refused oral medication (and had never received a conventional depot), two had failed to respond to conventional depots, one patient was said to be allergic to oil and one was transferred to local services already on treatment. Two further patients had chosen to receive RLAI after a discussion of the options available to them.

Who received it?

One patient was cared for by elderly services, two by learning disabilities services, and one by forensic services. The remaining 46 were in the care of adult services, ranging from intensive care through rehabilitation and assertive outreach to clinically stable out-patients. All had a psychotic illness, although not always schizophrenia; this is in line with the licensed indications for risperidone.

Dosage and clinical outcomes at 3 and 6 months

The mean dosage prescribed was 32 mg every 2 weeks at 3 months and 35 mg every 2 weeks at 6 months. Fourteen patients who completed 6 months of treatment were receiving 25 mg, six patients 37.5 mg and nine patients 50 mg. Patient outcomes at 3 and 6 months are shown in Table 1. There was no difference in mean dosage

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Table 1. Clinical outcomes at 3 months and 6 months

Outcome	Number of patients at 3 months	Number of patients at 6 months
Very much improved	1	4
Much improved	14	16
Minimally improved	16	6
No change	5	2
Treatment failures[1]	6	10
Refused[2]	8	12
Total	50	50

1. Patients whose mental state either failed to improve (if acutely ill) or deteriorated (if switched because of side-effects) causing the prescriber to change treatment.

2. Patients who actively refused medication or failed to keep appointments such that administration was too erratic to be effective.

between responders and non-responders. Patients who were very much or much improved at 3 months maintained this improvement at 6 months. Half of those rated as minimally improved at 3 months were very much or much improved at 6 months. The attrition rate at 6 months was 42%.

Other findings

Although data were not collected systematically, many patients remained on (and seemed to require) oral medication for longer than the 3-week lead-in period recommended by the manufacturer. By 6 months, all patients were receiving RLAI as antipsychotic monotherapy.

Providing supplies of RLAI to both in-patient units and community psychiatric nurse (CPN) bases in a large specialist mental health trust has been challenging. Systems for dealing with 'cold chain' products had not previously been in place: community mental health centres (CMHCs) did not routinely have a drug refrigerator or cool bags. Wastage was caused by RLAI being left unrefrigerated in CMHCs, leaking needles (packs do not contain a spare needle) and patients refusing their injection after the dose had been reconstituted. At a cost of £148 for each 37.5 mg dose (the mean dose used), the total wastage cost can be considerable.

The inflexibility of fixed doses and dosage intervals caused problems for some prescribers and patients.

Discussion

The majority of patients who were prescribed RLAI had a history of non-compliance with oral antipsychotics and had experienced intolerable neurological side-effects with conventional depot formulations. Prescribing in this way is entirely logical and in line with the guidance given by the National Institute for Clinical Excellence (2002). Only two patients could be described as having established treatment-resistant illness (both had previously developed agranulocytosis with clozapine), although it is possible that emerging treatment resistance was a problem in a minority of other patients. Given that treatment-resistant patients were not pre-selected and that it is commonly perceived that the use of depot preparations improves 'compliance', our response rate seems low and our attrition rate high.

Response

Risperidone long-acting injection has been shown to be superior to placebo in a 12-week randomised controlled trial (Kane *et al*, 2003), equivalent to oral risperidone in a 12-week randomised controlled trial (APC/DTC Briefing, 2002), and effective and relatively well tolerated in a 1-year open study. This is a fairly slim evidence base. Nothing is known about the efficacy of RLAI in comparison with conventional depots or how patients switched from conventional depot therapy fare. Just over half our cohort had made at least minimal clinical gains by 6 months, although the proportion achieving very good or good clinical outcomes was just 40%. Given the way that response was quantified, in that an improvement in neurological side-effects rather than an improvement in psychotic symptoms may have been the desired goal, this seems low.

Only half of those who achieved a very good or good clinical outcome at 6 months had done so by 3 months. If RLAI is to be prescribed, then at least 6 months treatment might be required to identify all responders. A fifth of patients were switched to another antipsychotic because the prescribing doctor judged that their mental state was either deteriorating (if previously stable) or failing to improve (if acutely unwell). The period of greatest risk seemed to be the first few months of treatment. This may be due to the pharmacokinetics of RLAI in that it takes at least 3 weeks after the first injection to achieve 'therapeutic' plasma levels of risperidone. The recommended 3-week period for supplementing RLAI with oral risperidone might not be adequate for all patients. Although data were not collected systematically, many patients in our cohort received (and seemed to require) additional oral treatment for up to 8 weeks after their first injection of RLAI. It is possible that our response rate might have been higher if prescribers had provided patients with oral antipsychotic cover for longer and continued RLAI for at least 6 months before switching to alternative antipsychotic agents.

Dose

The modal dose prescribed was 32 mg at 3 months and 35 mg at 6 months. Some patients did not like the inflexibility of both doses and dosage intervals. No negotiation is possible about 'small' dosage decreases as the whole contents of a vial have to be administered. Likewise, the frequency of administration cannot be decreased to every 3 or 4 weeks as an aid to maintaining a therapeutic alliance with the patient.

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Attrition rate

A systematic review has failed to find a difference in attrition rates between patients prescribed oral antipsychotic drugs and those prescribed depot formulations (Adams *et al*, 2001), although it is known that a quarter of those who are prescribed conventional depots are dissatisfied with their treatment (Walburn *et al*, 2001). It is possible that compliance rates are superior for depot preparations in the real world where compliance rates in general are likely to be lower than in clinical trials. At the very least, covert non-compliance is avoided. Falloon (1984) reported an 80% compliance rate with depots compared with 60% with oral antipsychotics. O'Ceallaigh & Fahy (2001) suggest that compliance rates with atypical depots may be superior.

By 6 months, over a fifth of our cohort had withdrawn from treatment after either actively refusing their injection or more passively failing to turn up for appointments or be accessible to their CPN. When added to the 20% of patients whose treatment was changed by the prescriber, 42% were no longer receiving RLAI 6 months after treatment was started. This is a higher attrition rate than the 35% seen during the 1-year open label licensing study conducted by the manufacturers (APC/DTC Briefing, 2002).

Use by forensic services

Forensic psychiatrists are frequent prescribers of conventional depot antipsychotics and, in a previous survey, indicated that they would use more atypical drugs if a depot preparation became available (Paton *et al*, 2002). However, only one patient from forensic services was prescribed RLAI. The reasons for this low local uptake rate are unknown.

Conclusions

In one mental health trust, 40% of patients who were prescribed RLAI had achieved good or very good clinical outcomes at 6 months, 18% fared poorly and were switched to alternative treatments, and 24% failed to comply. The remainder made minimal clinical gains. Supplementation with oral antipsychotic agents may be required for longer than the 3-week period recommended by the manufacturer and at least 6 months treatment with RLAI may be required to identify all responders. Although a welcome addition to the range of antipsychotic preparations available, RLAI is unlikely to replace conventional depot antipsychotic drugs in all patients. We have much to learn about how to optimise its use in clinical practice.

References

ADAMS, C. E., FENTON, M. K. P., QURAISHI, S., *et al* (2001) Systematic meta-review of depot antipsychotic drugs for people with schizophrenia. *British Journal of Psychiatry*, **179**, 290–299.

APC/DTC BRIEFING (2002) Long acting risperidone injection (Risperdal Consta). www.druginfozone.org

FALLOON, R. H. (1984) Developing and maintaining adherence to long-term drug-taking regimens. *Schizophrenia Bulletin*, **10**, 412–417.

GEDDES, J., FREEMANTLE, N., HARRISON, P., *et al* (2000) Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. *BMJ*, **321**, 1371–1376.

GUY, W. (1976) *ECDEU Assessment Manual for Psychopharmacology* (revised), p. 534. Rockville, MD: National Institute of Mental Health.

KANE, J. M., EERDEKENS, M., LINDENMAYER, J. P., *et al* (2003) Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. *American Journal of Psychiatry*, **160**, 1125–1132.

NATIONAL INSTITUTE OF CLINICAL EXCELLENCE (2002) *Guicance on the Use of Newer (Atypical) Antipsychotic Drugs for the Treatment of Schizophrenia*. Health Technology Appraisal 43. London: NICE.

NATIONAL SCHIZOPHRENIA FELLOWSHIP (2001) *A Question of Choice*. London: NSF.

O'CEALLAIGH, S. & FAHY, T. A. (2001) Is there a role for the depot clinic in the modern management of schizophrenia? *Psychiatric Bulletin*, **25**, 481–484.

PATON, C., GARCIA, J. A. & BROOKE, D. (2002) Use of atypical antipsychotics by consultant psychiatrists working in forensic settings. *Psychiatric Bulletin*, **26**, 172–174.

WALBURN, J., GRAY, R., GOURNAY, K., *et al* (2001) Systematic review of patient and nurse attitudes to depot antipsychotic medication. *British Journal of Psychiatry*, **179**, 300–307.

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