BJPsych | The British Journal of Psychiatry (2013) 203, 215–220. doi: 10.1192/bjp.bp.113.125807

Effect of prior treatment with antipsychotic long-acting injection on randomised clinical trial treatment outcomes

Thomas R. E. Barnes, Richard J. Drake, Graham Dunn, Karen P. Hayhurst, Peter B. Jones and Shôn W. Lewis

Background
It is uncertain whether antipsychotic long-acting injection (LAI) medication in schizophrenia is associated with better clinical outcomes than oral preparations.

Aims
To examine the impact of prior treatment delivery route on treatment outcomes and whether any differences are moderated by adherence.

Method
Analysis of data from two pragmatic 1-year clinical trials in which patients with schizophrenia were randomised to either an oral first-generation antipsychotic (FGA), or a non-clozapine second-generation antipsychotic (SGA, CUtLASS 1 study), or a non-clozapine SGA or clozapine (CUtLASS 2 study).

Results
Across both trials, 43% ($n = 155$) of participants were prescribed an FGA-LAI before randomisation. At 1-year follow-up they showed less improvement in quality of life, symptoms and global functioning than those randomised from oral medication. This difference was confined to patients rated as less than consistently adherent pre-randomisation. The relatively poor improvement in the patients prescribed an LAI pre-randomisation was ameliorated if they had been randomised to clozapine rather than another SGA. There was no advantage to being randomly assigned from an LAI at baseline to a non-clozapine oral SGA rather than an oral FGA.

Conclusions
A switch at randomisation from an LAI to an oral antipsychotic was associated with poorer clinical and functional outcomes at 1-year follow-up compared with switching from one oral antipsychotic to another. This effect appears to be moderated by adherence, and may not extend to switching to clozapine. This has implications for clinical trial design: the drug from which a participant is randomised may have a greater effect than the drug to which they are randomised.

Declaration of interest
T.R.E.B. has received honoraria from Lilly and Roche for speaking at educational meetings. K.P.H. has received assistance to attend educational meetings from Novartis and Lilly. P.B.J. was a member of a scientific advisory board for Roche. S.W.L. has received honoraria from Janssen for speaking at educational meetings.

Adherence to prescribed antipsychotic drug treatment is considered to be a crucial variable in predicting medium- to long-term clinical outcome in people with schizophrenia.[1] Since the 1970s, one approach to ensuring delivery of a prescribed drug, and monitoring medication adherence objectively, has been the use of antipsychotic long-acting intramuscular injections (LAIs: depot preparations), particularly to maintain remission.[2] The frequency of use of these preparations varies between countries, but in the UK, LAIs are prescribed for between a quarter and a third of people with schizophrenia, depending on the clinical setting.[3] Although some patients may express a preference for an LAI rather than oral antipsychotic medication,[4,5] many prescribers have concerns over the acceptability of LAI preparations for their patients.[6] Current UK treatment guidance recommends their use on the basis of patient preference and/or to avoid covert non-adherence.[7,8]

Despite strong clinical impressions, robust and consistent data confirming the superiority of LAIs over oral antipsychotic, preparations for relapse prevention in schizophrenia have not been forthcoming from synthesis of the available randomised controlled trials (RCTs).[9–14] But naturalistic cohort studies have revealed a superiority for LAIs over oral antipsychotics in preventing readmission to hospital or on all-cause discontinuation[1,15–18] and similar findings have emerged from mirror-image studies.[10,19,20] This discrepancy may partly reflect that RCTs may have a limited ability to identify differences between LAIs and oral antipsychotics because of their nature, being generally short term, selecting patients who are medication adherent[21] and reducing the likelihood of relapse and readmission to hospital because of the level and frequency of monitoring involved. Further, it has been argued that the clinical characteristics of the population of patients recruited into the RCTs may differ in critical ways from the population for whom such LAIs are prescribed in routine practice. This point was made in two recent papers reporting meta-analyses of relevant RCTs of relapse prevention in schizophrenia, one of which found LAIs had a 'clinically meaningful' superiority to oral antipsychotic drugs[11] and one which, although finding no overall advantage for LAIs over oral antipsychotics, found that, in older RCTs, first-generation antipsychotic (FGA) LAIs (mainly fluphenazine LAI) showed significant superiority.[14]

The present study involved the analysis of data collected in the context of two pragmatic clinical trials, CUtLASS 1[22] (Cost Utility of the Latest Antipsychotics in Severe Schizophrenia) and CUtLASS 2.[23] These trials tested antipsychotic medication in schizophrenia for which a change in medication was clinically indicated because of poor therapeutic response. The main finding of CUtLASS 1 was that, against expectations, clinical and functional outcomes at 1 year were no better in patients randomised to a second-generation antipsychotic (SGA) than those randomised to an FGA. The CUtLASS 2 study confirmed the superior effectiveness of clozapine over non-clozapine SGAs in people with treatment-resistant schizophrenia. A significant

proportion of participants across the two trials were receiving an FGA-LAI prior to randomisation. As all the patients who entered the trials switched from one medication to another, the data collected allowed us to test the following hypotheses: (a) switching from an FGA-LAI to an oral antipsychotic leads to poorer outcomes than switching from one oral to another; (b) switching from an FGA-LAI to an oral SGA protects against poor outcome, compared with an oral FGA; (c) switching to clozapine protects against poor outcome, compared with a non-clozapine SGA; and (d) differences in clinical outcomes between FGA-LAI and oral antipsychotic treatment are moderated by medication adherence.

Method

CUtLASS

Eligible patients for the CUtLASS 1 trial were aged 18–65 years, with a DSM-IV[24] schizophrenia or related (schizoaffective or delusional) disorder that had shown an inadequate clinical response to, or intolerance of, antipsychotic treatment, prompting their prescribing clinician to consider a change in treatment. Across five UK centres, those patients consenting to participate in CUtLASS 1 were randomised to either an FGA or a (non-clozapine) SGA. In CUtLASS 2, patients with a treatment-resistant illness, as defined by a documented poor response to sequential trials of two or more antipsychotics, were randomised to either a non-clozapine SGA drug or clozapine. Assessments (masked to treatment allocation) took place at baseline and at 12, 26 and 52 weeks following randomisation.

Measures

The primary outcome measure was the Heinrichs' Quality of Life Scale (QLS).[25] Secondary outcome measures included symptoms (Positive and Negative Syndrome Scale (PANSS),[26] Calgary Depression Scale for Schizophrenia (CDSS)),[27] social, occupational and psychological functioning (Global Assessment of Functioning Scale (GAF)),[24] attitudes to medication (Drug Attitude Inventory (DAI))[28] and adherence (Kemp Compliance Scale).[29] Non-neurological side-effects were measured using the Antipsychotic Non-Neurological Side-Effects Rating Scale (ANNSERS).[30,31] Extrapyramidal side-effects were assessed using the Extrapyramidal Side Effects Scale (EPSE),[32] the Barnes Akathisia Rating Scale (BARS)[33] and the Abnormal Involuntary Movement Scale (AIMS).[34]

Statistical analysis

The QLS score, PANSS total, PANSS positive subscale and GAF were modelled as outcomes, separately for CUtLASS 1 and 2. All were multilevel, mixed-effects models fitted using full information maximum likelihood, with unstructured covariance matrices and centre entered as a random effect, using the *xtmixed* command in Stata 11 for Windows. Binary variables representing randomisation (to FGA or SGA in CUtLASS 1; and clozapine or other SGA in CUtLASS 2) and prescription of an LAI before randomisation were entered as predictors. Interaction terms for LAI × time (indicating significant differences in improvement over follow-up for those previously prescribed an LAI) and LAI × randomisation × time (indicating whether randomisation to FGA, SGA or clozapine significantly altered any specific effect of LAI on follow-up) were included. Gender, age, ethnicity and square root of length of illness were included as potential confounders.

In CUtLASS 1, improvement in QLS over time was curvilinear (rather than a linear improvement with other outcomes) and in CUtLASS 2 improvement in PANSS total and positive subscales were curvilinear so quadratic terms were introduced to model the effects of time.

A moderator analysis of the effect of medication adherence was performed, using scores on the Kemp Compliance Scale from each assessment during the study. This is a single item rating of adherence and concordance scored 1–7, with higher scores indicating greater adherence to the treatment regimen. The baseline score referred to adherence with the pre-randomisation medication. *A priori* the scale was arbitrarily dichotomised into $\geqslant 6$ and $\leqslant 5$, a cut-off close to the median values in both CUtLASS 1 and CUtLASS 2, with those scoring >5 at all stages considered consistently adherent. This analysis was repeated using a score of >5 at baseline alone, to investigate whether confounding processes post-randomisation substantially affected the comparison. A final analysis examined the moderating effect of baseline DAI score, dichotomised at 10 for CUtLASS 1 and 6 for CUtLASS 2 (the mean values).

Results

Sample

The key demographic and clinical characteristics of participants in the two CUtLASS treatment trials are set out in Table 1. Categorical variables were compared using chi-squared tests and continuous variables compared using *t*-tests or Mann–Whitney tests for skewed variables. Analyses of the CUtLASS 1 data-set excluded five patients who were not receiving antipsychotic drug treatment at trial entry.

Antipsychotic drug treatment

Table 2 provides details of the antipsychotic medication prescribed at baseline, prior to study entry into the CUtLASS 1 and CUtLASS 2 trials, for those patients receiving an LAI pre-randomisation. In CUtLASS 1, 41% ($n=90$) of participants were receiving an LAI prior to randomisation. These were all FGA-LAIs. Of this LAI subgroup, 39 (43%) were co-prescribed an oral antipsychotic; patients in this subgroup were also more likely to receive more than one antipsychotic drug ($P<0.001$), to receive high-dose antipsychotic treatment (>1000 mg chlorpromazine equivalents: 11 (12%) LAI *v.* 6 (5%) non-LAI group, $P=0.035$) and be prescribed an anticholinergic agent (56 (62%) LAI *v.* 50 (38%) non-LAI group, $P<0.001$) compared with those not prescribed an LAI.

In CUtLASS 2, 48% of the sample ($n=65$) were being treated with an FGA-LAI at baseline assessment, prior to randomisation. As in CUtLASS 1, patients in this LAI subgroup were more likely at baseline to be receiving combined antipsychotics (29 (45%) of LAI *v.* 8 (11%) of non-LAI group, $P<0.001$).

Table 3 provides details of oral antipsychotic medication prescribed to the non-LAI subgroups before randomisation in CUtLASS 1 or CUtLASS 2. Fifteen (11%) patients in the CUtLASS 1 non-LAI subgroup and 8 (11%) of the CUtLASS 2 non-LAI group were prescribed more than one oral antipsychotic drug concurrently at baseline.

Outcome measures

Table 4 provides scores on the main outcome measures at baseline and at each of the three subsequent follow-up assessments for the pre-randomisation LAI and non-LAI groups in CUtLASS 1 and CUtLASS 2. In CUtLASS 1, clinicians selected in advance the specific FGA or SGA medication to be used depending on the result of randomisation. For FGAs, sulpiride was the most popular choice (50%, $n=58$), with an LAI (flupentixol, fluphenazine, zuclopenthixol) being selected in 7% ($n=8$) of cases. Excluding

Table 1 Key demographic and clinical characteristics of participant subgroups in the CUtLASS 1 and CUtLASS 2 trials

	Pre-randomisation LAI subgroup	Pre-randomisation non-LAI subgroup	*P*		
			χ^2	Mann–Whitney	*t*-test
CUtLASS 1					
n	90	132			
Gender, male: *n* (%)	58 (64)	92 (70)	0.412		
Age, years: mean (s.d.)	44.1 (10.1)	38.4 (11.3)			<0.001
Ethnicity, White: *n* (%)	67 (74)	101 (77)	0.724		
Illness duration, years: median	16.1	8.3		<0.001	
In-patient status, *n* (%)	18 (20)	69 (52)	<0.001		
Number of previous hospital admissions, median	3	2		<0.001	
CUtLASS 2					
n	65	71			
Gender, male: *n* (%)	44 (68)	49 (69)	0.868		
Age, years: mean (s.d.)	38.8 (10.8)	36.5 (11.6)			0.242
Ethnicity, White: *n* (%)	49 (75)	49 (69)	0.408		
Illness duration, years: median	11.9	10.5		0.159	
In-patient status, *n* (%)	33 (51)	43 (61)	0.251		
Number of previous hospital admissions, median	4	3		0.095	

LAI, long-acting injection.

Table 2 Antipsychotic medication prescribed to pre-randomisation long-acting injection (LAI) subgroups in the CUtLASS 1 and CUtLASS 2 trials

	CUtLASS 1 (*n* = 90)		CUtLASS 2 (*n* = 65)	
Drug	*n*	Mean dose, mg	*n*	Mean dose, mg
LAI (depot medication)				
Flupentixol decanoate	33	158 every 4 weeks	29	80 every week
Fluphenazine decanoate	22	97 every 3 weeks	13	74 every 2 weeks
Haloperidol decanoate	12	99 every 2 weeks	3	144 every 2 weeks
Pipotiazine palmitate	11	99 every 3 weeks	5	128 every 4 weeks
Zuclopenthixol decanoate	12	407 every 2 weeks	15	478 every 2 weeks
Adjunctive oral medication: daily dose				
Amisulpride	0		2	450
Chlorpromazine	13	204	12	288
Droperidol	3	57	0	
Flupentixol	0		1	12
Haloperidol	2	17	3	13
Loxapine	1	30	0	
Olanzapine	2	15	3	20
Prochlorperazine	1	15	0	
Risperidone	2	3	3	6
Sulpiride	3	533	4	850
Thioridazine	7	96	2	225
Trifluoperazine	5	18	1	10
Zuclopenthixol	1	10	1	20

the latter eight participants from the current analysis did not affect the results.

Multilevel modelling

CUtLASS 1: the effect of LAI

The LAI × time term was statistically significant for measured quality of life (QLS score). That is, by 1-year follow-up, the QLS score in those taking an oral antipsychotic before randomisation had improved 5.4 points (95% CI 1.8–9.0, $P = 0.003$) more than in those randomised from an LAI. There was no effect in this group of being randomised to either an FGA or SGA trial medication ($P > 0.70$). The LAI × time term was also statistically significant for PANSS score ($P = 0.03$). In those participants taking oral medication at baseline, mean total PANSS score at final follow-up had improved by 3.8 points (95% CI 0.8–7.2) more than in those patients who had been randomised from an LAI. Again, there was no significant effect of being randomised to an FGA or SGA ($P > 0.99$). On the PANSS positive subscale, there was no significant effect of LAI × time ($P > 0.47$). In terms of symptoms and function assessed by the GAF, LAI × time was also significant ($P = 0.008$). By final follow-up, those randomised from an oral drug improved 4.2 points (95% CI 1.1–7.4) more than those previously prescribed an LAI. There were no significant differences between FGA and SGA groups in improvement on any outcome over follow-up (i.e. LAI × time × randomisation).

CUtLASS 1: the effect of adherence

The analyses were repeated separately for participants who were consistently adherent (those scoring 6 or 7, where 7 is maximally adherent, on the Kemp Compliance Scale at each stage, as assessed by staff and raters) and participants who were inconsistently adherent (those scoring 5 or below, indicating at best passive acceptance of medication, at any point), to assess whether adherence moderated outcome. This showed that, in participants rated as consistently adherent ($n = 54$), those taking LAIs at baseline showed no less improvement than those taking orals on PANSS

Table 3 Oral antipsychotic medication prescribed to pre-randomisation non-long-acting injection subgroups in the CUtLASS 1 and CUtLASS 2 trials

	CUtLASS 1 ($n=132$)		CUtLASS 2 ($n=71$)	
Drug	*n*	Mean daily dose, mg	*n*	Mean daily dose, mg
Amisulpride	2	1000	5	770
Benperidol	0		1	0.75
Chlorpromazine	16	369	4	288
Droperidol	9	18	0	
Flupentixol	2	7	0	
Haloperidol	16	14	5	18
Olanzapine	21	14	23	16
Pimozide	2	13	1	8
Quetiapine	5	400	10	620
Risperidone	10	6	15	6
Sertindole	1	8	0	
Sulpiride	24	938	5	1150
Thioridazine	15	217	0	
Trifluoperazine	22	19	10	26
Zuclopenthixol	2	30	0	
No antipsychotic drug at baseline	5	–	0	–

Table 4 Assessment scores for pre-randomisation long-acting injection (LAI) and non-LAI groups in CUtLASS 1 and CUtLASS 2

	CUtLASS 1, mean (s.d.)		CUtLASS 2, mean (s.d.)	
Scale	Pre-randomisation LAI subgroup ($n=90$)	Pre-randomisation oral antipsychotic subgroup ($n=132$)	Pre-randomisation LAI subgroup ($n=65$)	Pre-randomisation oral antipsychotic subgroup ($n=71$)
Quality of Life Scale, total				
Baseline	45.0 (21.7)	42.5 (20.8)	36.9 (17.0)	38.1 (20.2)
Week 12	46.6 (18.2)	49.1 (20.1)	41.7 (18.5)	45.5 (18.3)
Week 26	48.7 (19.8)	51.1 (19.8)	44.2 (18.0)	47.9 (21.2)
Week 52	50.7 (21.2)	54.1 (20.5)	44.9 (17.6)	53.5 (20.3)
Positive and Negative Syndrome Scale, total				
Baseline	70.8 (16.6)	73.2 (16.9)	80.8 (18.8)	83.3 (21.8)
Week 12	69.9 (15.2)	67.7 (17.0)	73.8 (14.4)	70.7 (20.5)
Week 26	70.5 (17.2)	66.2 (16.0)	68.9 (16.1)	68.4 (20.1)
Week 52	66.7 (16.1)	64.3 (16.3)	67.7 (16.9)	63.8 (19.7)
Global Assessment of Functioning Scale				
Baseline	45.3 (15.6)	43.9 (13.5)	37.7 (12.3)	35.1 (14.8)
Week 12	47.3 (12.6)	49.5 (12.6)	42.8 (10.7)	42.1 (13.7)
Week 26	48.4 (14.7)	50.8 (12.0)	44.5 (9.9)	45.0 (13.4)
Week 52	50.7 (14.7)	53.7 (12.7)	45.7 (11.0)	51.4 (14.0)
Drug Attitude Inventory				
Baseline	10.8 (11.1)	8.3 (11.2)	7.1 (10.8)	5.6 (11.7)
Week 12	12.6 (11.3)	10.5 (11.4)	9.0 (11.2)	11.6 (11.1)
Week 26	12.8 (11.3)	10.4 (12.0)	11.1 (10.4)	11.4 (10.6)
Week 52	12.8 (12.2)	12.3 (10.2)	10.8 (11.7)	13.2 (10.5)

total ($P=0.14$), PANSS positive subscale ($P=0.35$) and GAF ($P=0.52$) scores, although they still showed significantly less improvement in QLS score than those previously taking tablets. Increase in the QLS was greatest in the initial stages, later flattening off. Correspondingly, the relative, negative effect of switching from an LAI was greatest in these early stages and best modelled as a curve, for example by adding a squared term. So by final follow-up, LAI × time ($P<0.001$) was −28.4 (95% CI −44.1 to −12.6) and LAI × time^2 ($P=0.01$) was 19.5 (95% CI 4.7–34.4).

On the other hand, among the subgroup of participants who were inconsistently adherent ($n=167$), those randomised from LAIs improved significantly less on most outcomes than those previously prescribed oral FGAs or SGAs. For the QLS score, switching from a pre-randomisation LAI reduced mean improvement by 4.1 points (95% CI 0.1–8.2, $P=0.044$); for PANSS total 3.6 points (95% CI –0.4 to 7.6, $P=0.08$); for GAF 5.2 points (95% CI 1.4–8.9, $P=0.007$). The PANSS positive subscale scores remained non-significantly different ($P=0.74$).

The analysis was repeated using only the baseline Kemp Compliance Scale scores, similarly dichotomised to consistently adherent and inconsistently adherent. The pattern of results was almost identical, although the negative effect of LAI × time on the QLS for the consistently adherent subgroup only reached $P=0.06$. Attitudes to medication measured by DAI also gave similar but less dramatic and consistent results (analyses available from the authors on request).

CUtLASS 2: the effect of LAI

As in the CUtLASS 1 data, both the QLS score and PANSS total score improved less over follow-up in those switched from an LAI ($n=65$): for the QLS by a mean of 4.9 points (95% CI 0.2–9.6, $P=0.04$) and for the PANSS total by a mean of 7.6

points (95% CI 0.6–14.5, $P=0.03$), a clinically significant effect. There was no significant effect of being randomised from an LAI to clozapine rather than other SGAs for the QLS ($P>0.21$), although for PANSS there was a trend to improve more on clozapine ($P=0.07$, mean 8.5 points, 95% CI –0.7 to 17.8). There was no significant effect of randomisation from an LAI on the PANSS positive subscale (LAI × time, $P>0.09$; LAI × randomised treatment × time, $P>0.33$). For global functioning (GAF score) too, those prescribed an LAI at baseline improved 11.2 points less over 1 year (95% CI –6.1 to –16.4, $P<0.001$) than those prescribed oral antipsychotics before randomisation. Clozapine compensated for this group effect (9.1 points, 95% CI 2.3–15.9, $P=0.009$), i.e. the group randomised from an LAI to clozapine were barely disadvantaged, unlike those randomised to other SGAs. Again, adherence as scored on the Kemp Compliance Scale had a moderating effect. In the small group of patients who were consistently adherent ($n=29$), pre-randomisation LAI prescription had no significant effect on change in the QLS ($P>0.39$), PANSS total ($P>0.96$), PANSS positive subscale ($P>0.85$) or GAF ($P>0.24$) scores. In those inconsistently adherent ($n=107$), being on an LAI at baseline reduced the final improvement in the QLS (by mean 6.7 points, 95% CI 1.2–12.1, $P=0.02$), positive symptoms (mean 9.3, 95% CI 1.8–16.9, $P=0.015$; with significant quadratic, time^2 term, mean −7.5, 95% CI −14.8 to −0.1, $P=0.046$) and GAF (mean 10.8, 95% CI 6.3–15.4, $P<0.001$); but had no significant effect on PANSS total ($P>0.35$). Using the baseline assessment of pre-randomisation adherence rather than identifying those rated adherent throughout the study again yielded similar results.

Baseline attitudes to medication (DAI score) had a similar moderating effect to adherence, although less uniform and marked (data available from the authors on request).

Discussion

For participants in the CUtLASS studies, there was an overall improvement in symptoms, function and quality of life, as measured by the QLS, over the 1-year follow-up period. However, as predicted, those prescribed an LAI before randomisation experienced statistically and clinically significantly less improvement in their QLS, PANSS and GAF scores than those randomised from oral medication. In CUtLASS 1, this effect is much larger than the effect of post-randomisation medication assignment (FGA or SGA): the antipsychotic preparation the participant is randomised from is more important than the antipsychotic they are randomised to. The hypothesis that this effect is moderated by a measure of medication adherence was supported. For those participants rated consistently adherent at baseline, receiving an LAI before randomisation made no significant difference to symptoms or function in either CUtLASS 1 or CUtLASS 2. In contrast, those participants who were rated as less consistently adherent in CUtLASS 1 did significantly worse if they were randomised from an LAI at baseline, compared with those randomised from oral medication. There was a similar finding in CUtLASS 2: the relative reduction in symptoms in the inconsistently adherent subgroup was not significantly ameliorated by assignment to clozapine as the study medication. This moderating effect of adherence suggests that the poorer outcomes in those receiving LAI at baseline was not due to any differences in agent or dosage from those receiving oral antipsychotic at baseline.

To summarise, our data reveal that switching from an LAI to an oral antipsychotic medication was a relatively unsuccessful strategy in those participants exhibiting inconsistent adherence to medication. Overall, individuals in the consistently adherent subgroup previously prescribed an LAI did as well as those previously taking oral drugs in CUtLASS 1 and 2; but it appears that in CUtLASS 2 those randomised from an LAI had better symptom improvement on clozapine than other SGAs.

Strengths and limitations

Perhaps the main strengths of this study are, first, that the participants had been recruited into a pragmatic study that had been designed to test medication effectiveness in a population representative of those who would receive such treatment in routine clinical practice, and second, that the participants were followed up for a year.

One limitation of the study is that the LAIs prescribed at baseline were all FGA-LAIs and any extrapolation of the findings to SGA-LAIs must be tentative. However, perhaps the main limitation is that the CUtLASS trials were not primarily designed to examine the type of treatment previously prescribed for the trial participants. Thus, one must be cautious in inferring that prior prescription of an LAI caused differences in outcome. It is likely that those participants prescribed LAIs before the trial differed from those prescribed oral medication on a range of clinical and illness variables. For example, poor adherence and more severe illness are possible indications for the prescription of an LAI. Such variables may be relevant to why those participants switching from an LAI have poorer outcomes than those switching from oral antipsychotics. But this finding might also partly reflect advantages of LAI medication that would be lost after switching to an oral drug: these include more predictable and stable serum drug levels, and regular scrutiny of the patient by the healthcare professional administering the LAI.

The analyses may not have accounted fully for these possible clinical differences between those prescribed an LAI and those receiving an oral antipsychotic pre-trial. Nevertheless, the predicted outcomes associated with pre-randomisation route of administration of antipsychotic medication were found, and the moderating effect of medication adherence was confirmed. The observed moderating effect of adherence suggests strongly that other possible explanations for the findings, such as the effectiveness of high dose or polypharmacy, more frequent in the baseline LAI group, were not the important factors.

Implications

The present study, as far as we are aware, represents the first attempt to examine the impact of prior treatment delivery route on outcome in an RCT. The findings suggest that the nature of previous antipsychotic medication in terms of delivery route should be taken into account in trials that involve randomisation to antipsychotic drug treatment at baseline. The type of medication that a participant is randomised from may be more important in determining outcome than the type of medication they are randomised to. Specifically, the consequences of switching from an LAI to an oral antipsychotic, other than clozapine, may be worse than switching from an oral drug.

Thomas R. E. Barnes, DSc, Centre for Mental Health, Imperial College, London, and West London Mental Health NHS Trust; **Richard J. Drake**, MRCPsych, PhD, Institute of Brain, Behaviour and Mental Health, University of Manchester, Manchester; **Graham Dunn**, PhD, Institute of Population Health, University of Manchester, Manchester; **Karen P. Hayhurst**, PhD, Institute of Brain, Behaviour and Mental Health, University of Manchester, Manchester; **Peter B. Jones**, MD, Department of Psychiatry, The University of Cambridge, and Cambridge and Peterborough NHS Foundation Trust, Cambridge; **Shôn W. Lewis**, MD, FMedSci, University of Manchester and Manchester Academic Health Sciences Centre, Manchester, UK

Correspondence: Thomas R. E. Barnes, Centre for Mental Health, Imperial College, 37 Claybrook Road, London W6 8LN, UK. Email: t.r.barnes@imperial.ac.uk

First received 3 Jan 2013, final revision 12 Apr 2013, accepted 17 Apr 2013

Funding

This study utilises data from the CUtLASS trials funded by NIHR Health Technology Assessment.

Acknowledgements

We would like to express our thanks to the following people who provided essential support to the CUtLASS trials: Alex Barrow, Candice Blackwell, Maria Clark, John Cooley, Peter Elton, Tracy Fay, Simon Foster, John Geddes, Maurice Gervin, Nerys Gooding, Tanya Hawthorn, Rhona Howitt, Fiona Hynes, Xinming Jin, Rob Kerwin, Fionnbar Lenihan, Glyn Lewis, Ahmed Mahmoud, Jennifer Massie, Paul Monks, Susie Morrow, Natasha Newbery, Eleanor Page, Lisa Riley, Paul Schofield, Joanne Shepherd, Patricia Smith, Emma Sowden, David Taylor, Helen Woodiwiss and Zhenhua Zhu.

References

1 Novick D, Haro JM, Suarez D, Perez V, Dittmann RW, Haddad PM. Predictors and clinical consequences of non-adherence with antipsychotic medication in the outpatient treatment of schizophrenia. *Psychiatry Res* 2010; **176**: 109–13.

2 Barnes TRE, Curson DA. Long term depot antipsychotics: a risk–benefit assessment. *Drug Saf* 1994; **10**: 464–79.

3 Barnes TRE, Shingleton-Smith A, Paton C. Antipsychotic long-acting injections: prescribing practice in the UK. *Br J Psychiatry* 2009; **195** (suppl): s37–42.

4 David AS, Adams C. Depot antipsychotic medication in the treatment of patients with schizophrenia: (1) meta-review; (2) patient and nurse attitudes. *Health Technol Assess* 2001; **5**: 1–79.

5 Patel MX, David AS. Why aren't depot antipsychotics prescribed more often and what can be done about it? *Adv Psychiatr Treat* 2005; **11**: 203–11.

6 Patel MX, Haddad PM, Chaudhry IB, McLoughlin S, Husain N, David AS. Psychiatrists' use, knowledge and attitudes to first- and second-generation antipsychotic long-acting injections: comparisons over 5 years. *J Psychopharmacol* 2010; **24**: 1473–82.

7 National Institute for Health and Clinical Excellence. *Schizophrenia: Core Interventions in the Treatment and Management of Schizophrenia in Adults in Primary and Secondary Care (Update), CG82*. NICE, 2009.

8 Barnes TRE. Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 2011; **25**: 567–620.

9 Adams CE, Fenton MKP, Quraishi S, David AS. Systematic meta-review of depot antipsychotic drugs for people with schizophrenia. *Br J Psychiatry* 2001; **179**: 290–9.

10 Haddad PM, Taylor M, Niaz OS. First-generation antipsychotic long-acting injections *v.* oral antipsychotics in schizophrenia: systematic review of randomised controlled trials and observational studies. *Br J Psychiatry* 2009; **195**: s20–8.

11 Leucht C, Heres S, Kane JM, Kissling W, Davis JM, Leucht S. Oral versus depot antipsychotic drugs for schizophrenia – a critical systematic review and meta-analysis of randomised long-term trials. *Schizophr Res* 2011; **127**: 83–92.

12 Rosenheck RA, Krystal JH, Lew R, Barnett PG, Fiore L, Valley D, et al. Long-acting risperidone and oral antipsychotics in unstable schizophrenia. *N Engl J Med* 2011; **364**: 842–51.

13 Leucht S, Tardy M, Komossa K, Heres S, Kissling W, Salanti G, et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *Lancet* 2012; **379**: 2063–71.

14 Kishimoto T, Robenzadeh A, Leucht C, Leucht S, Watanabe K, Mimura M, et al. Long-acting injectable vs oral antipsychotics for relapse prevention in schizophrenia: a meta-analysis of randomized trials. *Schizophr Bull* 2013; Jan 2 (Epub ahead of print).

15 Zhu B, Ascher-Svanum H, Shi L, Faries D, Montgomery W, Marder SR. Time to discontinuation of depot and oral first-generation antipsychotics in the usual care of schizophrenia. *Psychiatr Serv* 2008; **59**: 315–7.

16 Tiihonen J, Haukka J, Taylor M, Haddad PM, Patel MX, Korhonen P. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. *Am J Psychiatry* 2011; **168**: 603–9.

17 Grimaldi-Bensouda L, Rouillon F, Astruc B, Rossignol M, Benichou J, Falissard B, et al. Does long-acting injectable risperidone make a difference to the real-life treatment of schizophrenia? Results of the Cohort for the General study of Schizophrenia (CGS). *Schizophr Res* 2012; **134**: 187–94.

18 Bitter I, Katona L, Zámbori J, Takács P, Fehér L, Diels J, et al. Comparative effectiveness of depot and oral second generation antipsychotic drugs in schizophrenia: a nationwide study in Hungary. *Eur Neuropsychopharmacol* 2013; Mar 7 (Epub ahead of print).

19 Lambert T, Olivares JM, Peuskens J, Desouza C, Kozma CM, Otten P, et al. Effectiveness of injectable risperidone long-acting therapy for schizophrenia: data from the US, Spain, Australia, and Belgium. *Ann Gen Psychiatry* 2011; **10**: 10.

20 Peng X, Ascher-Svanum H, Faries D, Conley RR, Schuh KJ. Decline in hospitalization risk and health care cost after initiation of depot antipsychotics in the treatment of schizophrenia. *Clinicoecon Outcomes Res* 2011; **3**: 9–14.

21 Bowen J, Barnes TRE. The clinical characteristics of schizophrenic patients consenting and not consenting to a placebo-controlled trial. *Hum Psychopharmacol* 1994; **9**: 423–33.

22 Jones PB, Barnes TRE, Davies L, Dunn G, Lloyd H, Hayhurst KP, et al. Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia. *Arch Gen Psychiatry* 2006; **63**: 1079–87.

23 Lewis SW, Barnes TRE, Davies L, Murray RM, Dunn G, Hayhurst KP, et al. Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. *Schizophr Bull* 2006; **32**: 715–23.

24 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (4th edn) (DSM-IV)*. APA, 1994.

25 Heinrichs DW, Hanlon TE, Carpenter WT. The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. *Schizophr Bull* 1984; **10**: 388–98.

26 Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull* 1987; **13**: 261–76.

27 Addington D, Addington J, Schissel B. A depression rating scale for schizophrenics. *Schizophr Res* 1990; **3**: 247–51.

28 Hogan TP, Awad AG, Eastwood R. A self-report scale predictive of drug compliance in schizophrenics: reliability and discriminative validity. *Psychol Med* 1983; **13**: 177–83.

29 Hayward P, Chan N, Kemp R, Youle S, David A. Medication self-management: a preliminary report on an intervention to improve medication compliance. *J Ment Health* 1995; **4**: 511–7.

30 Yusufi B, Mukherjee S, Flanagan R, Paton C, Dunn G, Page E, et al. Prevalence and nature of side effects during clozapine maintenance treatment and the relationship with clozapine dose and plasma concentration. *Int Clin Psychopharmacol* 2007; **22**: 238–43.

31 Ohlsen RI, Williamson R, Yusufi B, Mullan J, Irving D, Mukherjee S, et al. Interrater reliability of the Antipsychotic Non-Neurological Side-Effects Rating Scale measured in patients treated with clozapine. *J Psychopharmacol* 2008; **22**: 323–9.

32 Simpson G, Angus J. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand* 1970; **45**: 11–9.

33 Barnes TR. A rating scale for drug-induced akathisia. *Br J Psychiatry* 1989; **154**: 672–6.

34 Guy W. *ECDEU Assessment Manual for Psychopharmacology. Revised DHEW Pub. (ADM)*. National Institute for Mental Health, 1976.

Effect of prior treatment with antipsychotic long-acting injection on randomised clinical trial treatment outcomes

Thomas R. E. Barnes, Richard J. Drake, Graham Dunn, Karen P. Hayhurst, Peter B. Jones and Shôn W. Lewis

BJP 2013, 203:215-220.
Access the most recent version at DOI: 10.1192/bjp.bp.113.125807