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Partial compliance with long-acting paliperidone palmitate and impact on hospitalization: a 6-year mirror-image study

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Abstract

Background: Previous studies showed a linear correlation between partial compliance with an oral antipsychotic medication and hospitalisation risk among patients with schizophrenia. Long-acting injections (LAIs) may significantly improve adherence and reduce relapse in patients with psychosis. The aim of this study was to evaluate the relationship between the level of compliance with 1-monthly paliperidone palmitate (PP1M) and hospitalisation rates.

Methods: This was a naturalistic, mirror-image study examining retention, compliance and hospitalisation rates 3 years pre- and 3 years post-PP1M initiation. Compliance was divided in three groups: full (no missed dose/year), good (6–11 injections/year), poor (<6 injections/year).

Results: A total of 173 patients suffering from a severe mental illness (70% with a diagnosis of schizophrenia and 30% with other diagnoses) were included; 77% of patients continued PP1M for 1 year, 66% for 2 years and 55% for 3 years. Of the 95 patients who remained on PP1 throughout the 3 years of follow up, 81% showed full, 13% good, and only 6% poor compliance. In the patients who were fully compliant, the mean number of hospital admissions decreased from 1.34 to 0.43, and the mean number of bed days from 82 to 19 days per patient 3 years before and 3 years after PP1M initiation ($p < 0.001$). It is noteworthy that the reductions in hospital stay were statistically significant for the group of patients with full compliance but not for the other two groups. In fact, patients with poor compliance demonstrated higher hospitalisation rates both before and after PPM1 initiation. These findings were similar in the subgroup of patients with schizophrenia who continued treatment for 3 years ($n = 68$).

Conclusion: There was a direct association between partial compliance and re-hospitalisation; fully compliant patients maintained the best outcomes in terms of reduced bed use following PPM1 initiation.

Keywords: hospitalisation, long-acting antipsychotics, paliperidone, partial compliance, schizophrenia

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Introduction

Partial compliance with antipsychotic medication is a common and serious problem in patients with schizophrenia, which increases with the duration of treatment.[1,2] Previous evidence has shown a direct correlation between partial compliance with an oral antipsychotic medication and hospitalisation risk among patients with schizophrenia across a continuum of compliance behaviour.[3,4] Tolerability is inseparably linked to patient compliance but second generation antipsychotic medications – although representing a heterogeneous class of drugs with broad differences in the degree of tolerability profiles – have been shown to be more acceptable to patients.[5] Furthermore, long-acting injections (LAIs) are known to reduce relapse and hospitalisation rates and the risk of nonadherence compared with oral antipsychotic medication in routine clinical practice.[6–9]

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However, treatment compliance with depot and long-acting antipsychotic medication appears to be often considered as an all-or-nothing phenomenon rather than a range of compliance behaviours. This may partly explain the lack of studies assessing the effects of partial compliance on treatment outcomes. The aim of this study was to evaluate the relationship between impact of the level of compliance with 1-monthly paliperidone palmitate (PP1M) on subsequent discontinuation and hospitalisation rates.

Methods

This is a naturalistic, independent, mirror-image study that took place in West London NHS Trust (WLHT). The study was approved by the department for audit (project number 1295). Patients were included if they were initiated on PP1M following a clinical decision between April 2011 and March 2015 and received treatment as usual.

Demographic data and other clinical information were obtained from the patients' electronic records, including diagnosis, retention and discontinuation rates, reasons for switching as well as the length and number of admissions in the 3 years prior to and post initiation of PP1M. As had been the case in previous studies,[10,11] the duration of the time from initiation to discharge was excluded from the total count of bed days post initiation if patients were started on PP1M in an inpatient setting. Information about the patients' compliance with PP1M was collected and measured by the number of depot treatments that were given in 1 year. Compliance was divided in three groups: full (no missed dose/year), good or $\geqslant$50% (6–11 injections/year), poor or $<$50% (1–5 injections/year).

Statistical analysis

Statistical Product and Service Solutions (SPSS) statistical software was used to perform statistical analysis. Descriptive statistics were used to summarise demographic and diagnostic information. Numbers and lengths of inpatient admissions were compared in a within-patient analysis. The non-normality of the distribution was ascertained by the Shapiro–Wilk test of normality, and Wilcoxon signed rank test for paired data was used to test the frequency and duration of hospital admissions before and after PP1M initiation. A non-parametric Friedman test of difference was conducted to compare bed usage after treatment with PP1M across the different levels of compliance; p values of 0.05 were used to determine significance.

Results

Of the 173 patients included in the study, 120 (70%) patients had a primary diagnosis of schizophrenia and 53 (30%) had schizoaffective disorder, bipolar affective disorder or other diagnoses. In total, 77% of patients continued PP1M for 1 year, 66% for 2 years and 55% for 3 years. Full details of the demographic and clinical characteristics as well as discontinuation rates and reasons and hospitalisation rates 3 years before and 3 years after treatment initiation of the total cohort and the groups of patients with schizophrenia and other diagnoses have been detailed in a previous publication.[12] The focus of this brief report is to evaluate the actual level of compliance of this patient population and its potential effects on number and length of admissions.

Compliance rates

Out of 173 patients, 122 patients (71%) were fully compliant, 21 (12%) were generally compliant and 13 patients (7%) were poorly compliant. The discontinuation rate at 3 years was 37% for patients with full, 33% with good and 70% with poor compliance.

Of the 95 patients who remained on PP1 throughout the 3 years of follow up, 81% were wholly compliant, 13% were 50% or over compliant and 6% were below 50% compliant. The compliance rates were the same for the subgroup of patients with schizophrenia ($n = 68$) who continued for the whole 3 years (Table 1).

Impact of level of compliance on hospital admissions

As previously reported, the whole patient group ($n = 95$) who continued with PP1M for 3 years – and regardless of the level of compliance – displayed significant reductions in the number and length of hospital admissions.[12] However, the current analysis demonstrates that the decline in hospitalisations yields statistically significance only for those patients that were fully compliant and not for those with good or poor compliance (Figures 1 and 2).

Specifically, for the fully compliant group, the median number of admissions dropped from 1.0 in the 3 years before to 0.0 in the 3 years after PP1M

initiation, whereas the mean number of admissions significantly decreased from 1.34 to 0.43 ($p=0.000$, Wilcoxon signed rank test). Similarly, median bed days fell from 30.5 days to 0.0 days and the mean number of bed days from 82 pre-PP1M to 19 post-PP1M initiation ($p=0.000$, Wilcoxon signed-rank test). For the patients with good compliance, mean number of admissions fell from 1 to 0.58 ($p=0.20$, Wilcoxon signed rank test) and mean length of admissions from 125 to 40 ($p=0.06$, Wilcoxon signed rank test).

Finally, the group with poor compliance demonstrated the highest hospitalisation rates both before and after PPM1 initiation and minimal reductions in mean number (2.17–1.67; $p=0.14$, Wilcoxon signed rank test) and duration of admissions (141–123 days; $p=0.67$, Wilcoxon signed rank test). In fact, the group of patients with schizophrenia and poor compliance performed the worst across all groups, showing the same mean number of admissions before and after treatment with PP1M (1.75) and even a higher number of mean bed days in the 3 years post initiation that is, 114 *versus* 161 bed days ($p=0.71$, Wilcoxon signed rank test) (Figure 3).

Furthermore, a Friedman test of difference was conducted to compare the number and length of admissions after treatment with PP1M across the different levels of compliance for the full patient group that completed 3 years on treatment. This rendered a Chi-square value of 5.94 for number of admissions and 10.74 for length of admissions. These had *p*-values of 0.05 and 0.005, respectively.

Table 1. Compliance rates of patients who continued on PP1M for 3 years.

Compliance rates at 3 years	100%	⩾50%	<50%
All patients ($n=95$)	81% (77/95)	13% (12/95)	6% (6/95)
Patients with schizophrenia ($n=68$)	81% (55/68)	13% (9/68)	6% (4/68)

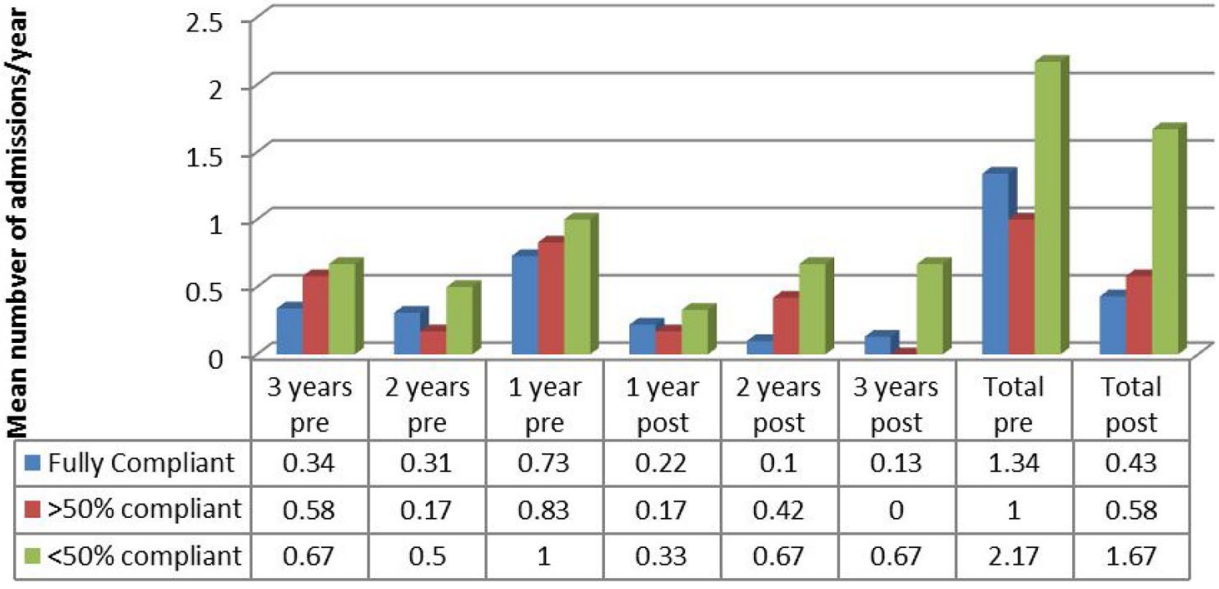
PP1M, 1-monthly paliperidone palmitate.

Discussion

To our knowledge, this is the first study to report on the level of compliance with long-acting antipsychotic medication and the effects on hospitalisation.

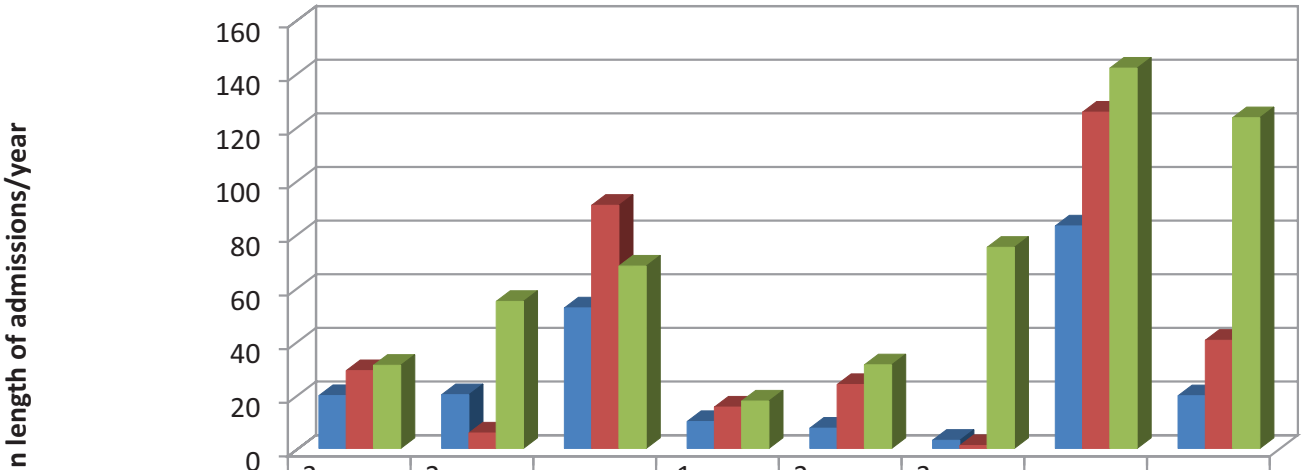
The overall compliance with PP1M was sizable, with more than two-thirds of this naturalistic cohort fully compliant. Poor compliance was a strong indicator of subsequent discontinuation as these patients were twice as likely to have completely discontinued PP1M at 3 years as compared with patients with full or good compliance.

In the primary analysis of patients who continued treatment for 3 years ($n=95$), we reported a



	3 years pre	2 years pre	1 year pre	1 year post	2 years post	3 years post	Total pre	Total post
Fully Compliant	0.34	0.31	0.73	0.22	0.1	0.13	1.34	0.43
>50% compliant	0.58	0.17	0.83	0.17	0.42	0	1	0.58
<50% compliant	0.67	0.5	1	0.33	0.67	0.67	2.17	1.67

Figure 1. Impact of level of compliance on mean number of admissions (per patient/per year and total 3 years pre and post PP1M initiation).
PP1M, 1-monthly paliperidone palmitate.



	3 years pre	2 years pre	1 year pre	1 year post	2 years post	3 years post	Total pre	Total Post
Fully compliant	19.7	20.03	52.4	10.03	7.55	3.03	82.97	19.64
>50% compliant	29	5.75	90.67	15.42	23.83	1.08	125.42	40.33
<50% compliant	31	54.83	68	17.67	31.17	75	141.83	123.33

Figure 2. Impact of level of compliance on mean length of admissions (per patient/per year and total 3 years pre and post PP1M initiation).
PP1M, 1-monthly paliperidone palmitate.

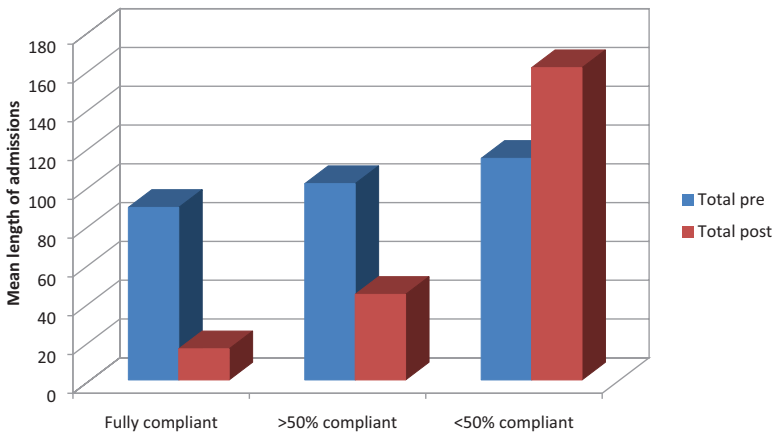


Figure 3. Length of admissions 3 years pre and post PP1M initiation according to rates of compliance in patients with schizophrenia.
PP1M, 1-monthly paliperidone palmitate.

substantial reduction in length and frequency of admission that was maintained over a 3-year period following the initiation of PP1M.[12] The current analysis, however, reveals a strong correlation between the actual level of compliance and the number and length of admissions. The fully compliant group of patients demonstrated the best outcomes when comparing bed use 3 years before and 3 years after PP1M initiation with a statistical significant decrease in both number and length of hospital admissions (Figures 1 and 2) and with more than half of the patients having no admission during 3 years follow up. On the other hand, the group with poor compliance demonstrated the highest hospitalisation rates both before and after PPM1 initiation. The subgroup of patients with schizophrenia who continued treatment for 3 years ($n = 68$) showed similar outcomes as above (Figure 3). Furthermore, there were statistically significant between group differences in outcomes according to the different levels of compliance when comparing hospitalisations during the follow up period.

There are no studies specifically evaluating the correlation between the level of compliance with depot/LAI antipsychotics and the effects on hospitalisation rates. However, partial compliance with oral antipsychotic medication has been previously associated with increasing risk of relapse in the long-term treatment of schizophrenia. For example, data from a 1-year cohort study of over 4000 patients with schizophrenia receiving antipsychotic therapy demonstrated that even small gaps in therapy (1–10 days) increased the

likelihood of hospitalisation two-fold, whereas larger gaps in therapy (⩾30 days) increased the likelihood of hospitalisation approximately four-fold.[3] Lower compliance with oral antipsychotic medication was associated with a greater risk of hospitalisation over and above any other risk factors for hospitalisation. Similarly, a study that utilised pharmacy records to assess compliance reported that hospitalisation rates were lower for those who were compliant (14%) than for those who were partially compliant (24%) or non-compliant (35%).[13] A further 1-year, observational study in over 60,000 patients with schizophrenia that used medication possession ratio (MPR) as a pharmacy-based measure of compliance demonstrated that decreasing MPR was associated with a progressive increase in admission rates. These ranged from 8.3% for an MPR of 0.9–1.0 (i.e. patients had sufficient medication 90% of the time), to rates greater than 20% for patients with an MPR of 0.5. It was estimated that an MPR 0.8 was associated with a two-fold greater risk of hospitalisation compared with those patients who were fully compliant with medication. Once admitted, poorly compliant patients had more hospital days than those who had good compliance.[14]

It is striking that the above findings were very much in line with the results of our study, despite the fact that when patients on depot/LAIs stop medication, plasma levels decrease more slowly than with oral formulations, allowing for earlier intervention and, thus, lowering the probability of rebound symptoms or of a relapse occurring as rapidly.[15] These results bear significant clinical implications as they not only stress the, more or less expected, difference in treatment outcomes between patients with good and poor compliance but also between patients with good *versus* patients with full compliance.

Furthermore, the findings suggest that patients who do not achieve satisfactory responses to treatment may be experiencing partial compliance problems rather than medication efficacy problems. Therefore, full compliance should not be assumed when patients receive long-acting injectable antipsychotic medication, and steps should be taken to further improve concordance where needed. To this end, less frequently administered LAIs, such as the 3-monthly formulation, may offer an interesting treatment alternative that could be considered in minimising the likelihood of partial compliance.

Limitations of the study include its observational, open, non-comparative design as well as the potential variation in the quality of electronic records.

Conclusion

Partial compliance with antipsychotic therapy has been shown to be directly related to rates of re-hospitalisation. Partial compliance with LAIs was associated with a poorer prognosis: the lower the level of compliance the higher the number and length of admissions.

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Conflict of interest statement

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Contributors

S. Pappa was responsible for the study concept and design. S. Pappa and K. Mason were responsible for data extraction, statistical analysis and drafting the manuscript. Both authors were responsible for critical revision of the manuscript and have accepted the final version.

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