A retrospective observational study of the effectiveness of Paliperidone Palmitate on acute inpatient hospitalization rates

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Summary:

This retrospective mirror-image observational study aimed to establish the effects of the long-acting antipsychotic injection Paliperidone Palmitate (PP) on acute inpatient hospitalization rates. We utilized routinely collected clinical data to compare the number and length of acute patient admissions one year pre and post initiation of PP. A single cohort of 66 patients with a diagnosis of schizophrenia and who had received monthly injections of PP for at least one year were included in the analysis. The mean number of acute inpatient admissions fell from 0.86 in the year before PP initiation to 0.23 in the following year (p=0.001), and there was a numerical but non-significant decrease in the number of bed days from 32.48 to 31.22 over the study duration. The median number of bed days in the year before PP initiation was 20, and in the year after initiation it was 0. The median number of admissions also fell from 1 to 0 during the same period. The results of the study should be treated cautiously but suggest that patients with a diagnosis of schizophrenia who continue treatment with PP over 12 months experience a significant reduction in numbers of hospital admissions compared to the previous year.

Keywords:

Antipsychotic, paliperidone, mirror image study, schizophrenia, hospitalizations

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Introduction

Schizophrenia is a severe mental illness that often requires treatment with antipsychotic medication for long periods in order to minimize the distress associated with symptoms and reduce the likelihood of relapse (Jablensky et al., 1992; Ascher-Svanum et al., 2006). Increases in the number of relapses and subsequent hospitalizations are closely associated with worse long-term patient outcomes (Falkai et al., 2006) and increased health care costs (Polsky et al., 2006). Due to these negative outcomes relapse prevention is a key therapeutic aim in the treatment of schizophrenia and antipsychotic medication plays a significant role (Olivares et al., 2013). Although antipsychotic medications can improve symptoms, patient non-adherence with oral formulations of antipsychotics is very common and this is associated with a much higher chance of relapse (Byerly et al., 2007). Some studies have shown that compared to oral medication the use of long-acting typical and atypical antipsychotic injections can improve treatment adherence and potentially reduce readmission rates over the longer term (Edwards et al., 2005; Haddad et al., 2009).

Numerous long-acting atypical antipsychotic injections are now available for use, but the evidence about their effectiveness in terms of reducing numbers and lengths of hospitalizations is somewhat mixed. Within some prospective observational studies atypical long acting injections have been shown to reduce relapse rates and readmissions to hospital when compared to oral antipsychotics (Olivares et al., 2009; Chue et al., 2005), whilst some longer-term controlled studies show no benefit of long-acting atypical injections over oral medications (Macfadden et al., 2010; Rosenheck et al., 2011).

Different observational studies exploring the effectiveness of the same atypical antipsychotic drug have also produced some equivocal findings. For example, a number of studies have

measured the impact of long-acting risperidone injections on patient hospitalization rates; some of these studies have shown that it is effective in reducing inpatient stays (Taylor et al., 2008), whilst others show an increase of admission days post initiation (Young and Taylor, 2006; Taylor and Cornelius, 2010).

Long-acting Paliperidone Palmitate (PP) injection is an atypical antipsychotic licensed for the treatment of schizophrenia and as it has been only relatively recently available there are few studies that explore its effectiveness. PP has been licensed for use in the UK since early 2011 and has been used our clinical setting since June 2011. Clinical trials have demonstrated the efficacy of PP in controlled research studies (Bishara, 2010), and a naturalistic observational cohort study suggests that PP was relatively well tolerated by patients, with 65% of 200 patients still receiving the drug after one year (Attard et al., 2013). Only limited information is published about PP's effectiveness in reducing the length and number of hospital admissions in real-life clinical practice. One such study conducted by Taylor and Olofinjana (2014) recently demonstrated through a 12 month prospective, non-interventional, observational study that the use of PP resulted in significant reductions in the number and length of hospital admissions per patient per year.

Taylor and Olofinjana' s 2014 study was conducted within a NHS Trust which provides mental health (MH) services to patients with a different ethnic demographic profile (compared to our patient population) and who were primarily residing in an inner city area; due to this the results are not directly generalisable to our more rural/suburban clinical setting. Therefore, the current study aims to establish the potential effects of PP treatment in terms of effects on acute inpatient hospitalization rates in our MH trust.

Methods

The study was carried out in one NHS MH trust located in southern England and was approved by the Trusts' clinical audit and effectiveness office as a service evaluation on the 9th September

2014. All data were anonymised and held securely in line with the Trust's data protection policies.

Key Inclusion Criteria

We screened the electronic record data of male and female patients with a diagnosis of schizophrenia, aged 18-65 and who had been treated with PP in both acute inpatient and out-patient settings. Patients with a minimum of one year's clinical data pre-initiation of PP recorded on the electronic patients record system and a minimum of one year's clinical data recorded post-initiation of PP were included in the analysis. Patients were only included if they had completed at least 12 months treatment with PP. Patients' data also excluded if PP was being used out-of-license or if patients were switched from Clozapine to PP (as PP is not indicated for patients who are treatment resistant).

Data Collection

The number of acute inpatient admissions and number of associated bed days in the one year before and one year after PP initiation were obtained from patients' records. We also gathered a range of other clinical and demographic data that were recorded in the patients' electronic notes, including: gender, ethnicity, age at initiation of PP, employment status, marriage status, treatment setting, duration of contact with mental health services and responsiveness to PP treatment (as defined by HoNOS scores; Wing et al., 1998). We wanted to focus on the use of acute inpatient services so we excluded all hospital admissions and related bed days that related to either forensic or specialist rehabilitation settings both pre and post PP initiation. Our clinical rationale for excluding these admissions was that the lengths of hospitalization and criteria for patient discharge were more likely to be related to court restrictions and the need for ongoing rehabilitation than the effects of antipsychotic treatment.

Primary (a-priori) analysis approach

The primary endpoint for this study was the mean number of hospital admissions and number of bed days 1 year preceding initiation of PP and mean number of hospital admissions and number of bed days in the one year following initiation of PP. Whether the patient was initiated in the community or in the hospital setting, the mirror date was set at 2 weeks after PP initiation (see figure 1). We chose 14 days as our mirror point in an attempt to account for the bed days that may be associated with efficacy failure of the previous drug. This is an important consideration because it is estimated that 58% percent of costs incurred during the first week on a new antipsychotic are most likely due to treatment ineffectiveness of the previous antipsychotic rather than the failure of the newly introduced medication (Faries et al., 2009). Our strategy was based on reports that generally a satisfactory therapeutic response to antipsychotics is usually seen within two weeks after initiation (Glick et al., 2009; Leucht et al., 2005) and that on average PP reaches peak plasma concentration around 13 days after the first injection into the deltoid muscle (Sheehan et al, 2012).

Post-hoc sensitivity analyses:

For reasons of transparency and comparability with previously published similar studies we also adopted an additional post-hoc sensitivity analyses strategy which is the same as that described by Taylor and Olofinjana (2014). In this secondary analysis we used the date of PP initiation as the mirror point for all outpatients, but for patients who started on PP as an inpatient we compared the mean hospitalizations rates pre PP with the mean number in the year following discharge from the index admission (effectively discounting bed days from the post PP calculation where they were part of the index admission– see figure 2).

Data analysis strategy:

Data were analysed using the IBM SPSS statistical package version 21 (IBM Corp, 2012). The distribution of numbers of admissions and bed days was non-normal as shown by the

histograms and Normal Q-Q plot. This was additionally confirmed by the skewness and kurtosis indexes of the variables as well as the corresponding Kolmogorov-Smirnov and Shapiro-Wilk tests of normality. We therefore used Wilcoxon signed rank tests and bootstrap paired sample t-tests to test the null hypothesis of no difference in number of admissions and bed-days pre and post PP-initiation.

Results

Data were initially retrieved from 148 patients. After applying our inclusion criteria a final sample of 66 patients was retained. The main reasons for excluding cases related to not having a minimum of one year pre and sufficient post PP initiation data recorded or patients not having a diagnosis of schizophrenia. All PP discontinuers were excluded from the analysis in line with the study inclusion criteria. We initially intended to explore responsiveness to PP treatment (as defined by routinely recorded HoNOS scores), but unfortunately due to sparseness of data and the irregularity in which scores were recorded we were left with only 9 patients' data that could be analyzed and we therefore had to abandon this approach due to the small sample size.

Demographic and clinical characteristics

Most patients included in this study were white, single males that were either unemployed or defined as being long-term sick. The mean age of the participants was 40.86 and they had been in contact with MH services on average for almost 10 years. Demographic information about the sample is summarized in table 1.

Number of Admissions and Bed days

The average number of admissions in the year pre-PP initiation was 0.86, SD= 0.88, while the average number of admissions in the year post-PP initiation was 0.23, SD=0.55 and the median

number of admissions reduced from 1 to 0 over the study duration. The Wilcoxon test (<0.0001) and the Bootstrap paired sample t-test (0.64, 95% CI: 0.42, 0.85, p=0.001) showed a significant reduction in the number of admissions post PP initiation.

There was a numerical decrease in mean number of bed days from one year before PP initiation 32.48 (SD=44.76) to one year post-PP initiation 31.22 (SD=53.33). The median number of bed days decreased from 20 to 0. The Wilcoxon test (p=0.50) and the Bootstrap t-test (mean diff= 1.26, 95% CI: 10.66, 13.95, p=0.84) showed a non-significant difference in bed days between pre and post initiation.

The histograms (figure 3) illustrate that although many patients had a reduction in bed days, some patients with long admissions post PP initiation have skewed the mean. These 7 patients had long admissions for a number of reasons, including: disturbed behavior requiring intensive care, psychiatric co-morbidities, complex psychiatric needs and placement issues. The distribution of pre-post differences in number of admissions and bed days was not significantly different across both treatment settings and genders.

Sensitivity analysis

Please see table 2 for comparison of pre and post PP differences according to the two different approaches used to calculate before and after outcomes. The post-hoc sensitivity analyses used the same analysis tests as our primary approach and results in significant improvements in average admissions from 0.86 to 0.23 and a reduction in annual bed days from 26.77 before PP, to 11.23 in the following year (Wilcoxon p=0.003; Bootstrap t-test= 15.55, CI: 3.66, 28.86; p=0.016).

Discussion

Our primary endpoint analysis shows that the monthly administration of long-acting injectable PP in 66 patients with schizophrenia over one year was associated with a significant reduction in the mean number of acute inpatient admissions when compared to the previous year. There was also a numerical (but non-significant) decrease in average number of bed days during the year following PP initiation. The median number of admissions reduced from 1 to 0 in the year after starting PP and median amount of bed days decreased from 20 to 0 over the same period. The primary strategy that we used to calculate pre and post outcomes is less likely to favour the new drug than those studies which discount all index admission days from the post treatment group by inserting the mirror point at the point of discharge (i.e. Taylor and Olofijana, 2014), and therefore our results could arguably present a realistic, but more conservative picture.

Due to a current lack of evidence from observational naturalistic studies of PP it is problematic to compare and contrast our results with previously published outcomes. Direct comparisons of our findings with those of Taylor and Olofijana (2014) are also complicated by the differing clinical contexts, their larger sample size, inclusion of non-continuers of PP and some of the demographic characteristics of participants. Despite the ethnicity and percentage of women patients being very different in our study compared to Taylor and Olofijana's, there are some other demographics that are very comparable: 45% of participants in each study were initiated in outpatient settings, the mean duration of illness in both studies was around nine years and the average age was 41 in our study (vs. 43 years). Their primary analysis method involved comparing the average yearly rates/lengths of hospitalization during the three years prior to PP initiation with the mean number of hospitalizations post PP, and for patients initiated as inpatients this was calculated from the year after the point of discharge from an index admission. This approach produced significant reductions in the mean number of bed days (38.78 to 23.09) and admissions (0.67 to 0.49) after starting PP. However, using a mirror point inserted at the time of initiation for all patents they found a significant reduction in admissions of 0.67 to 0.51 and an increase of bed days from 38.78 to 56.75; findings which are less favourable to the results from our primary endpoint analysis. Similarly to Taylor and Olofijana's study the median number of admissions and bed days in our study was 0 in the year after PP

initiation (irrespective of which method was used to calculate this). When we adopted the same method of analysis as Taylor and Olofijana's study, our results show a similar reduction in bed days and a greater reduction in the number of admissions for patients continuing PP for at least a year following initiation.

The findings resulting from our sensitivity analysis highlight how the varying mirror-points used to calculate before and after outcomes can have a large influence on results. Our post-hoc analysis is certainly more likely to favour the new drug as it discounts all index admission bed days from the post PP calculations; as could be expected this shows large and significant reductions in hospitalizations in the year following PP. A number of other researchers (i.e. Taylor and Olofijana, 2014; Faries et al., 2009) have also demonstrated that the different strategies used in mirror-image studies to handle acute-service use occurring just after an antipsychotic medication change can have profound effects on study findings. Strategies that compare the bed days in the year pre-initiation with the bed days in the year after patients are discharged from the index admission tend to favour the new drug. Whilst approaches that attribute bed days from an index admission to post-treatment immediately following initiation are likely to underestimate positive effects of the new antipsychotic (Taylor and Olofijana, 2014; Faries et al., 2009). Therefore, using a mirror point of two weeks post initiation seemed an appropriate way for us to address these issues and minimize the risk of over or underestimating the effects of PP on hospitalizations.

Given the relatively expensive cost of PP it is worth considering its potential cost-effectiveness in our study population. A widely used and broadly illustrative method to estimate cost effectiveness is to calculate savings made on reduced hospitalizations and offset these against the costs of medication (Bernardo, et al., 2006), but as our sensitivity analysis shows, in this study the results will vary based in the approach used to measure before and after effects.

The average monthly maintenance dose of PP in this study is 102mg (excluding any additional amounts for the initial loading dose) and therefore the conservative annual purchase cost per

patient is around £3,769. Given that the Trust's average acute admission length is 31.4 days, and one acute bed day in our Trust is costed at £375, this equates to an average cost of £11,775 per admission; as the bootstrap t-test results in our primary endpoint analysis show a significant reduction of 0.64 admissions per patient in the year following PP, this suggests an average saving of £7,536, which clearly outweighs the annual PP cost of £3,769. Our sensitivity analysis (which is arguably more likely to favour PP) additionally demonstrates a significant reduction of 15.55 bed days post initiation and this equates to a potential acute hospitalization cost saving of £2,062 per patient initiated on PP (£5,831 - £3,769). These (albeit somewhat crude) calculations suggest that PP is largely cost-effective in our clinical setting.

Due to the limitations of the retrospective observational study design and the relatively small sample size our results should be treated with caution, particularly as any changes in rates and lengths of admissions may be due to numerous possible extraneous influences. We cannot certainly establish that PP reduces the number of acute inpatient admissions or is more/less superior to other medications because this is an uncontrolled study without a comparison group. We did not include a control arm in our study and therefore changes in the bed days and admission rates observed may be a reflection of background variation irrespective of treatment. We were also not able to access information about which drugs patients were prescribed before initiation and therefore we are not able to identify any potential associations between these and differences in rates of hospitalization.

All data originated from patients who were adherent with their prescribed PP treatment over at least a year, and as a result our findings will be more positive than those studies which include data from patients who have discontinued treatment. Additionally, patients were not randomised to receive treatment and therefore decisions about which patients were selected by prescribers to start PP is likely to have been based on their perceived increased likelihood of who would respond to the drug. Similarly, local prescribing guidelines suggest that only patients who have had an adequate previous response to oral risperidone, which is almost identical to PP in its pharmacological properties (Spina and Cavallaro, 2008; Bishara and Taylor, 2008) can

be considered for PP; this may have resulted in patients who respond to, but are non-adherent with oral risperidone starting PP and therefore the patients included in this study are likely to represent the most responsive population.

Despite these limitations, our findings are based on routinely collected clinical data in a real-world setting. We have not excluded any patients with substance misuse or physical/mental health co-morbidities, there were no major changes in hospital admission policy or bed closures which are likely to have affected rates of hospitalization, and therefore the results may plausibly reflect the naturalistic outcomes of patients with schizophrenia who continue PP treatment within the MH trust studied. Although our results are promising, in order to more certainly measure the effects of PP on the use of acute inpatient services future observational studies should consider using a prospective design with a comparison group.

In conclusion, this observational study suggests that PP initiation in patients with a diagnosis of schizophrenia (and who continue with regular monthly injections over 12 months) is likely to be associated with a significant reduction in the number of hospital admissions when compared to the previous year.

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Conflicts of interest:

DB has received research funding from Janssen and Pfizer's, and has received honorarium payments for consultancy from Lundbeck, BMS and Janssen. JS has received research funding from Janssen and honoraria for consultancy work from Janssen, Lundbeck, Astra-Zeneca, Sunovion, BMS and Lilly. SH and DM have no conflicts of interest.

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Table 1: Demographics of participants

Parameter	N= 66
Age at initiation of PP:	
Mean (SD),	40.86 (12.87)
Range	18-65
Duration of contact with services at PP initiation (N=63)	
Mean (SD),	9.70 (8.20)
Range	1-50
Sex, n (%)	
Male	47 (71)
Female	19 (29)
Ethnicity, n (%)	
Black	3 (4.5)
White	50 (76.7)
Other	10 (15.0)
Unknown	3 (4.5)
Care setting at PP initiation, n (%)	
Inpatient	36 (54.5)
Outpatient	30(45.5)
Employment status, n (%)	
Employed	4 (6.1)
Unemployed	21 (31.8)
Long-term sick	23 (34.8)
Other	18 (27.2)
Marital status, n (%)	
Married	5 (7.5)
Single	42 (63.6)
Divorced/Separated/Other	19 (28.7)

Table 2: Differences between 1 year pre and post PP hospitalization rates

Analysis strategy *(n=66)*	Admissions in one year before PP *Mean (SD)* *Median*	Admissions in one year after PP *Mean (SD)* *Median*	Bootstrap t test :mean difference, (95%CI), p value Wilcoxon signed rank test (p)	Bed days in one year before PP *Mean (SD)* *Median*	Bed days in one year after PP *Mean (SD)* *Median*	Bootstrap t test :mean difference, (95%CI), p value Wilcoxon signed rank test (p)
(i) Primary end point analysis	0.86 (0.88) (Median = 1)	0.23 (0.55) (Median = 0)	0.64 (0.42, 0.85) P=0.001* p<0.0001*	32.48 (44.76) (Median = 20)	31.22 (53.33) (Median = 0)	1.26 (-10.66,13.95) p=0.84 p=0.50
(ii) Sensitivity analysis	0.86 (0.88) (Median =1)	0.23 (0.55) (Median =0)	0.64 (0.42, 0.85) P=0.001* p<0.0001*	26.77 (43.17) (Median =12)	11.23 (30.41) (Median =0)	15.55 (3.66, 28.86) p=0.016* p= 0.003*

(i) Mirror point inserted at 14 days post PP initiation for all patients (see figure 1).
(ii) Mirror point inserted at PP initiation for all patients and index admission bed days post PP disregarded for patients initiated whilst in hospital (see figure 2).
* Significant at P<0.05
PP, Paliperidone Palmitate

Figure 1: Schematic representation of primary end-point analysis (all patients)

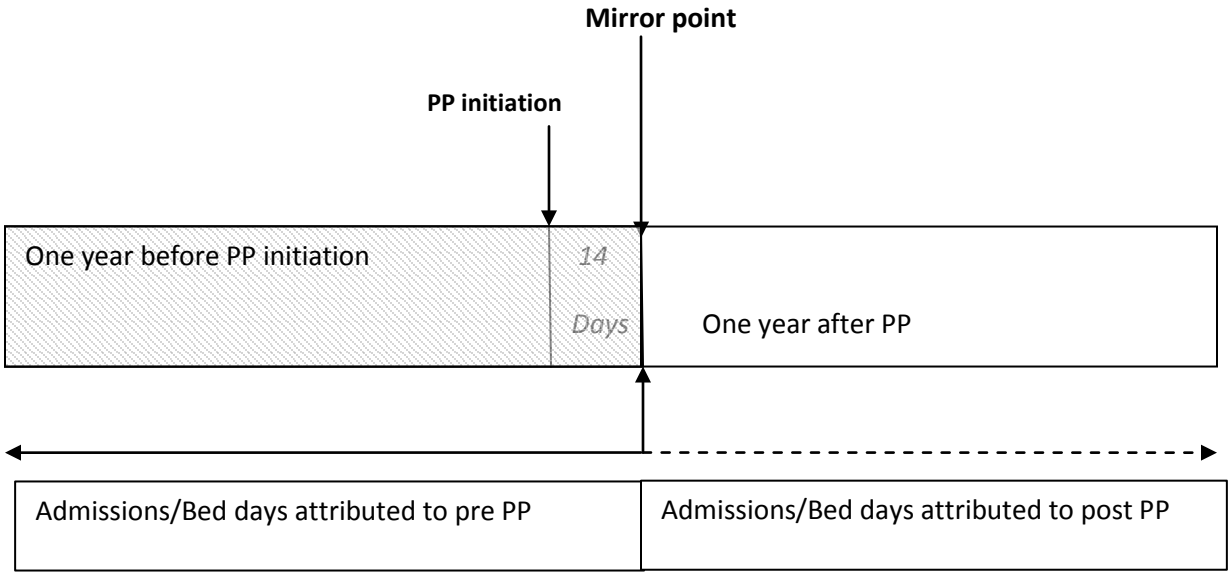

Figure 2: Schematic representation of sensitivity analysis (Inpatient initiated patients)

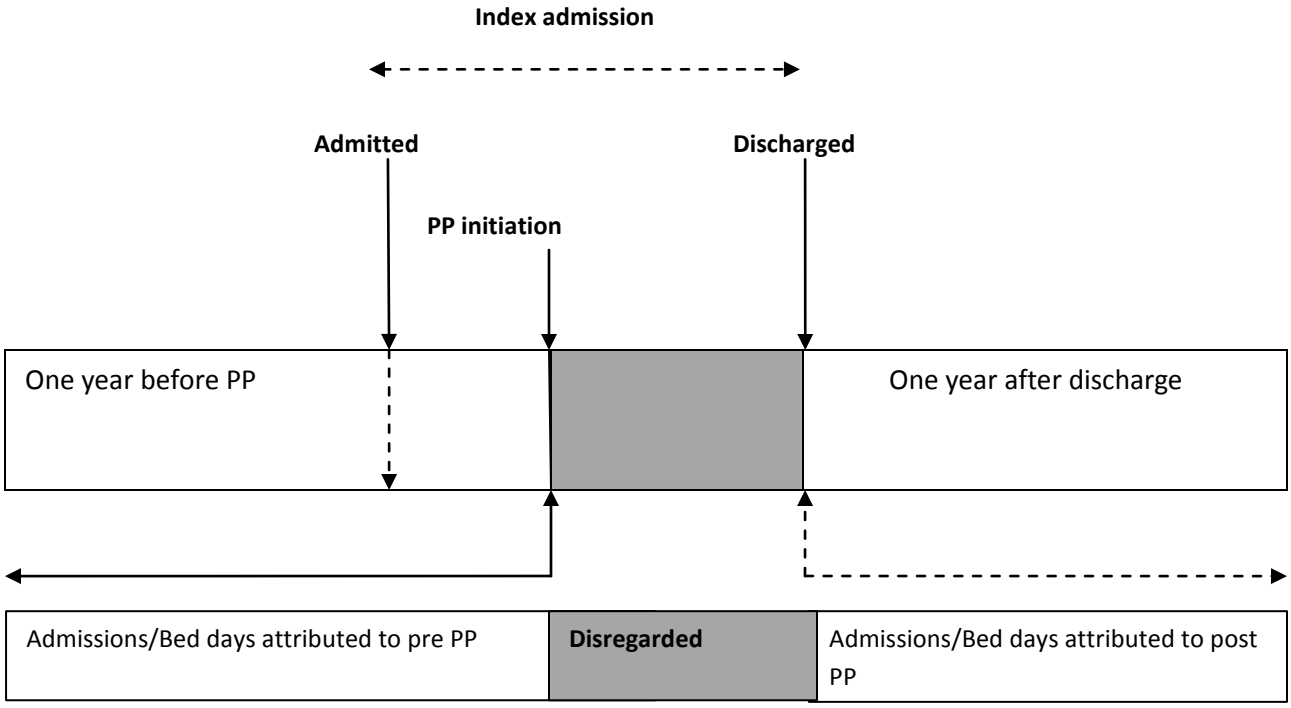

Figure 3: Histograms of bed day's pre and post PP