OPEN

# A retrospective observational study of the effectiveness of paliperidone palmitate on acute inpatient hospitalization rates

Daniel Bressington[a,c], Jon Stock[b], Sabina Hulbert[c] and Douglas MacInnes[c]

**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 1 year before and 1 year after 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 1 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 nonsignificant 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 because of the limitations of the study design but suggest that patients with a diagnosis of schizophrenia who continue treatment with PP over 12 months experience a significant reduction in hospital admissions compared with the previous year.** ***Int Clin Psychopharmacol*** **30:230–236** 

**International Clinical Psychopharmacology** 2015, **30**:230–236

**Keywords: antipsychotic, hospitalizations, mirror-image study, paliperidone, schizophrenia**

[a]School of Nursing, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong, [b]Kent and Medway NHS and Social Care Partnership Trust, Maidstone and [c]Canterbury Christ Church University, Canterbury, UK

Correspondence to Daniel Bressington, PhD, School of Nursing, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong
Tel: +852 2766 6408; fax: +852 2364 9663;
e-mail: dan.bressington@polyu.edu.hk

**Received** 11 January 2015 **Accepted** 16 March 2015

## Introduction

Schizophrenia is a severe mental illness that often requires treatment with antipsychotic medication for long periods 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 healthcare costs (Polsky *et al.*, 2006). Because of 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 nonadherence 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 with 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 evidence on their effectiveness in terms of reducing the number and length of hospitalization 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 with oral antipsychotics (Chue *et al.*, 2005; Olivares *et al.*, 2009), whereas 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), whereas others show an increase in the number of admission days after 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 its availability is relatively recent there are few studies that explore its effectiveness. PP has been licensed for use in the UK since early 2011 and has been used in our clinical setting since June 2011. Clinical trials





DOI: 10.1097/YIC.0000000000000077

have demonstrated the efficacy of PP in controlled research studies (Bishara and Taylor, 2008), 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 1 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 (2014) study was conducted within an NHS Trust that provided mental health (MH) services to patients with a different ethnic demographic profile (compared with our patient population) and who were primarily residing in an inner city area; because of this the results are not directly generalizable 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 9 September 2014. All data were anonymized and held securely in line with the Trust's data protection policies.

### Key inclusion criteria

We screened the electronic records of male and female patients with a diagnosis of schizophrenia, aged 18–65 years, who had been treated with PP in both acute inpatient and outpatient settings. Patients with a minimum of 1 year's clinical data recorded before initiation of PP on the electronic patients' record system and with a minimum of 1 year's clinical data recorded after initiation of PP were included in the analysis. Patients were included only if they had completed at least 12 months of treatment with PP. Patients' data were also excluded if PP had been used out-of-license or if patients had been 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 1 year before and 1 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 sex, ethnicity, age at initiation of PP, employment status, marital status, treatment setting, duration of contact with MH 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 and therefore excluded all hospital admissions and related bed days that related to either forensic or specialist rehabilitation settings both before and after PP initiation. Our clinical rationale for excluding these admissions was that the length 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 the initiation of PP and mean number of hospital admissions and number of bed days in the 1 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 (Fig. 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% of costs incurred during the first week on a new antipsychotic are most likely due to treatment ineffectiveness of the previous antipsychotic rather than 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 2 weeks of initiation (Leucht *et al.*, 2005; Glick *et al.*, 2009) and that on average PP reaches peak plasma concentration around 13 days after the first injection into the deltoid muscle (Sheehan *et al.*, 2012).

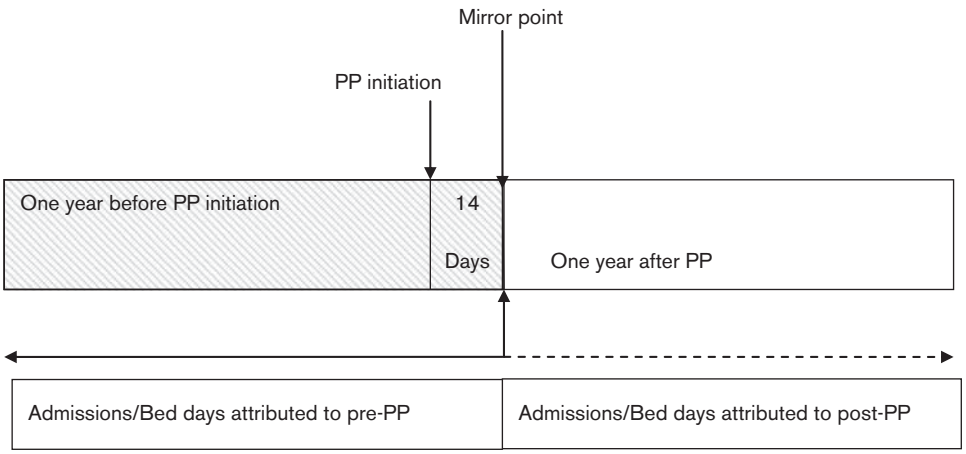
### Post-hoc sensitivity analyses

For reasons of transparency and comparability with previously published similar studies we also adopted an additional post-hoc sensitivity analysis strategy that was 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 before 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 Fig. 2).

### Data analysis strategy

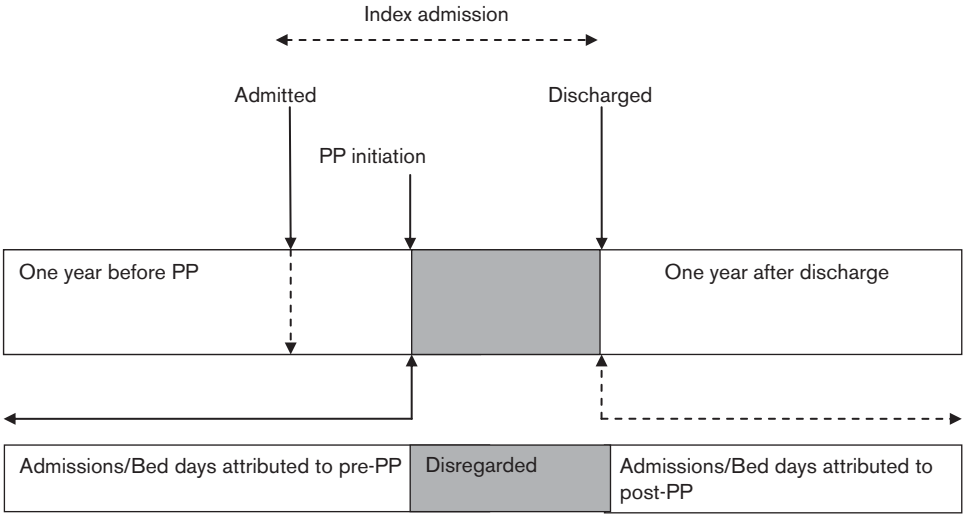
Data were analyzed using the IBM SPSS statistical package, version 21 (IBM Corp., 2012). The distribution of numbers of admissions and bed days was non-normal, as shown by the histograms and normal Q-Q plot. This was additionally confirmed by the skewness and kurtosis indices of the variables, as well as the corresponding Kolmogorov–Smirnov and Shapiro–Wilk tests of normality. We therefore used Wilcoxon signed rank tests

**Fig. 1**




Schematic representation of primary endpoint analysis (all patients). PP, paliperidone palmitate.

**Fig. 2**




Schematic representation of sensitivity analysis (inpatient initiated patients). PP, paliperidone palmitate.

and bootstrap paired sample *t*-tests to test the null hypothesis of no difference in number of admissions and bed days before and after 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 were related to not having a minimum of 1 year pre-PP initiation data and having insufficient post-PP initiation data or absence of 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 because of sparseness of data and the irregularity in which scores were recorded we were left with only nine patients' data for analysis and therefore had to abandon this approach because of the small sample size.

### Demographic and clinical characteristics

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

**Table 1 Demographics of participants**

| Parameter at initiation of PP | $N=66$ |
|---|---|
| Age | |
| Mean (SD) | 40.86 (12.87) |
| Range | 18–65 |
| Duration of contact with services ($N=63$) | |
| 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 [*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) |

PP, paliperidone palmitate.

### Number of admissions and bed days

The average number of admissions in the year before PP initiation was 0.86, SD = 0.88, whereas the average number of admissions in the year after PP initiation was 0.23, SD = 0.55; 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% confidence interval (CI): 0.42–0.85, $P=0.001$] showed a significant reduction in the number of admissions after PP initiation.

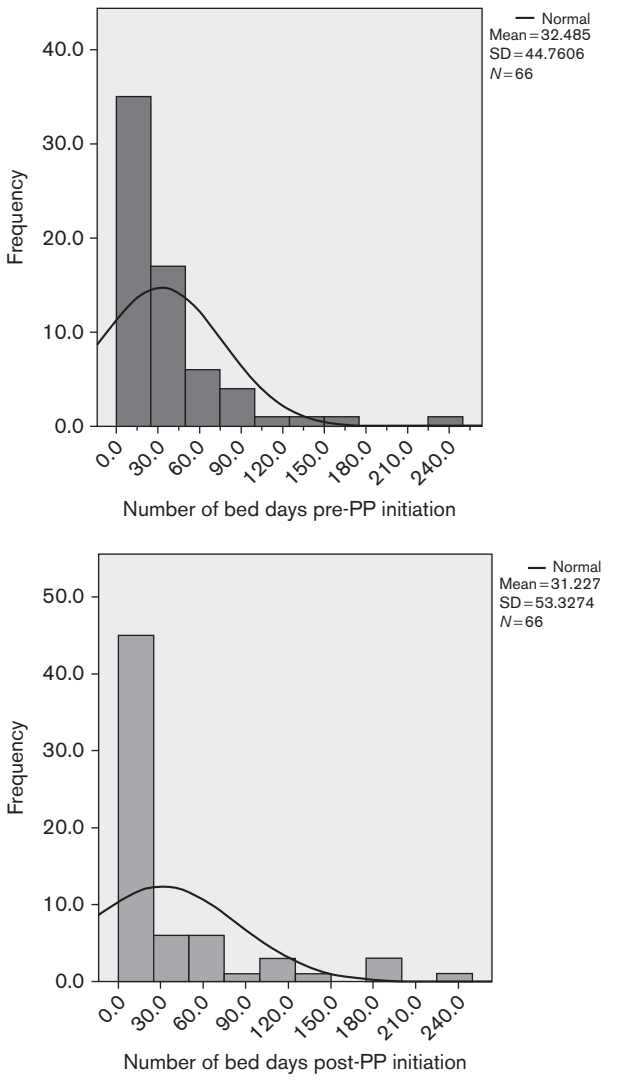
There was a numerical decrease in the mean number of bed days from 1 year before PP initiation (32.48; SD = 44.76) to 1 year after PP initiation (31.22; SD = 53.33). The median number of bed days decreased from 20 to 0. The Wilcoxon test ($P=0.50$) and the Bootstrap *t*-test (mean difference = 1.26, 95% CI: 10.66–13.95, $P=0.84$) showed a nonsignificant difference in bed days between preinitiation and postinitiation.

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

### Sensitivity analysis

Please see Table 2 for comparison of pre-PP 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 showed 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, 95% CI: 3.66–28.86; $P=0.016$).

**Fig. 3**




Histograms of bed days before and after PP. PP, paliperidone palmitate.

## Discussion

Our primary endpoint analysis shows that the monthly administration of long-acting injectable PP in 66 patients with schizophrenia over 1 year was associated with a significant reduction in the mean number of acute inpatient admissions when compared with the previous year. There was also a numerical (but nonsignificant) decrease in the average number of bed days during the year following PP initiation. The median number of admissions

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

| Analysis strategy ($n=66$) | Admissions in 1 year before PP Mean (SD) Median | Admissions in 1 year after PP Mean (SD) Median | Bootstrap *t*-test: mean difference (95% CI), *P* value Wilcoxon signed rank test (*P*) | Bed days in 1 year before PP Mean (SD) Median | Bed days in 1 year after PP Mean (SD) Median | Bootstrap *t*-test: mean difference (95% CI), *P* value Wilcoxon signed rank test (*P*) |
|---|---|---|---|---|---|---|
| (i) Primary endpoint 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 to 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 after PP initiation for all patients (Fig. 1).
(ii) Mirror point inserted at PP initiation for all patients and index admission bed days after PP disregarded for patients initiated while in hospital (Fig. 2).
CI, confidence interval; PP, paliperidone palmitate.
*Significant at $P<0.05$.

reduced from 1 to 0 in the year after starting PP and the median number of bed days decreased from 20 to 0 over the same period. The primary strategy that we used in order to calculate preoutcomes and postoutcomes is less likely to favor the new drug compared with those studies that discounted all index admission days from the post-treatment group by inserting the mirror point at the point of discharge (i.e. Taylor and Olofinjana, 2014), and therefore our results could arguably present a realistic, but more conservative, picture.

Because of a current lack of evidence from observational naturalistic studies of PP it is difficult to compare and contrast our results with previously published outcomes. Direct comparisons of our findings with those of Taylor and Olofinjana (2014) are also complicated by the differing clinical contexts, their larger sample size, inclusion of noncontinuers of PP, and some of the demographic characteristics of the participants. Despite the ethnicity and percentage of women patients being very different in our study compared with the study by Taylor and Olofinjana (2014), 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 9 years, and the average age was 41 years in our study (vs. 43 years). Their primary analysis involved comparing the average yearly rates/lengths of hospitalization during the 3 years before PP initiation with the mean number of hospitalizations after 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 in the number of bed days from 38.78 to 56.75 – findings that are less favorable to the results from our primary endpoint analysis. Similarly to the study by Taylor and Olofinjana (2014) 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 the study by Taylor and Olofinjana (2014), our results show a similar reduction in the number of 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 favor 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. Faries *et al.*, 2009; Taylor and Olofinjana, 2014) 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 number of bed days in the year before initiation with the number in the year after patients are discharged from the index admission tend to favor the new drug, whereas approaches that attribute bed days from an index admission to post-treatment immediately after initiation are likely to underestimate the positive effects of the new antipsychotic (Faries *et al.*, 2009; Taylor and Olofinjana, 2014). Therefore, using a mirror point of 2 weeks after initiation seemed an appropriate way for us to address these issues and minimize the risk of overestimating 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 for estimating cost effectiveness is the calculation of savings made on reduced hospitalizations and offsetting these against the costs of medication (Bernardo, *et al.*, 2006), but as our sensitivity analysis shows, in this study, the results will vary based on the approach used to measure before and after effects.

The average monthly maintenance dose of PP in this study is 102 mg (excluding any additional amounts for the initial loading dose) and therefore the conservative annual purchase cost per patient is around £3769. Given that the Trust's average acute admission length is 31.4 days, and one acute bed day in our Trust costs £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 £7536, which clearly outweighs the annual PP cost of £3769. Our sensitivity analysis (which is arguably more likely to favor PP) additionally demonstrates a significant reduction of 15.55 bed days after initiation and this equates to a potential acute hospitalization cost saving of £2062 per patient initiated on PP (£5831–£3769). These (albeit somewhat crude) calculations suggest that PP is largely cost effective in our clinical setting.

Because of 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 establish with certainty 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. As we did not include a control arm in our study the changes in the number of bed days and admission rates observed may be a reflection of background variations occurring 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 that included data from patients who had discontinued treatment. In addition, patients were not randomized 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, 2007; Bishara and Taylor, 2008), can be considered for PP; this may have resulted in patients who respond to, but are nonadherent 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/MH comorbidities; there were no major changes in hospital admission policy or bed closures that are likely to have affected the 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.

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 with the previous year.

## Acknowledgements

This study was funded by unrestricted investigator-initiated grant from Janssen UK.

### Conflicts of interest

D.B. has received research funding from Janssen and Pfizer, and has received honorarium payments for consultancy from Lundbeck, BMS, and Janssen. J.S. has received research funding from Janssen and honoraria for consultancy work from Janssen, Lundbeck, AstraZeneca, Sunovion, BMS, and Lilly. For the remaining authors there are no conflicts of interest.

## References

Attard A, Olofinjana O, Cornelius V, Curtis V, Taylor D (2013). Paliperidone palmitate long-acting injection – prospective year-long follow-up of use in clinical practice. *Acta Psychiatr Scand* **130**:46–51. *DOI: 10.1111/acps.12201.*

Ascher-Svanum H, Faries DE, Zhu B, Ernst FR, Swartz MS, Swanson JW (2006). Medication adherence and long-term functional outcomes in the treatment of schizophrenia in usual care. *J Clin Psychiatry* **67**:453–460.

Bernardo M, Ramón Azanza J, Rubio-Terrés C, Rejas J (2006). Cost-effectiveness analysis of schizophrenia relapse prevention : an economic evaluation of the ZEUS (Ziprasidone-Extended-Use-In-Schizophrenia) study in Spain. *Clin Drug Investig* **26**:447–457.

Bishara D, Taylor D (2008). Upcoming agents for the treatment of schizophrenia: mechanism of action, efficacy and tolerability. *Drugs* **68**:2269–2292.

Byerly MJ, Nakonezny PA, Lescouflair E (2007). Antipsychotic medication adherence in schizophrenia. *Psychiatr Clin North Am* **30**:437–452.

Chue P, Llorca P, Duchesne I, Leal A, Rosillon D, Mehnert A (2005). Hospitalization rates in patients during long-term treatment with long-acting risperidone injection. *J Appl Res Clin Exp Ther* **5**:266.

Edwards NC, Locklear JC, Rupnow MF, Diamond RJ (2005). Cost effectiveness of long-acting risperidone injection versus alternative antipsychotic agents in patients with schizophrenia in the USA. *Pharmacoeconomics* **23**:75–89.

Falkai P, Wobrock T, Lieberman J, Glenthoj B, Gattaz WF, Moller HJ (2006). World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, part 2: long-term treatment of schizophrenia. *World J Biol Psychiatry* **7**:5–40.

Faries DE, Nyhuis AW, Ascher-Svanum H (2009). Methodological issues in assessing changes in costs pre- and post-medication switch: a schizophrenia study example. *Cost Eff Resour Alloc* **7**:11.

Glick ID, Bossie CA, Alphs L, Canuso CM (2009). Onset and persistence of antipsychotic response in patients with schizophrenia. *J Clin Psychopharmacol* **29**:pp. 542–547.

Haddad PM, Taylor M, Niaz OS (2009). First-generation antipsychotic long-acting injections v. oral antipsychotics in schizophrenia: systematic review of randomised controlled trials and observational studies. *Br J Psychiatry Suppl* **52**:S20–S28.

IBM Corp. (2012). *IBM SPSS Statistics for Windows, version 210*. Armonk, NY: IBM Corp.

Jablensky A, Sartorius N, Ernberg G, Anker M, Korten A, Cooper JE, *et al.* (1992). Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization ten-country study. *Psychol Med Monogr Suppl* **20**:1–97.

Leucht S, Busch R, Hamann J, Kissling W, Kane JM (2005). Early-onset hypothesis of antipsychotic drug action: a hypothesis tested, confirmed and extended. *Biol Psychiatry* **57**:1543–1549.

Macfadden W, Ma YW, Thomas Haskins J, Bossie CA, Alphs L (2010). A prospective study comparing the long-term effectiveness of injectable risperidone long-acting therapy and oral aripiprazole in patients with schizophrenia. *Psychiatry (Edgmont)* **7**:23–31.

Olivares JM, Rodriguez-Morales A, Diels J, Povey M, Jacobs A, Zhao Z, *et al.*, e-STAR Spanish Study Group (2009). Long-term outcomes in patients with schizophrenia treated with risperidone long-acting injection or oral antipsychotics in Spain: results from the electronic Schizophrenia Treatment Adherence Registry (e-STAR). *Eur Psychiatry* **24**:287–296.

Olivares JM, Sermon J, Hemels M, Schreiner A (2013). Definitions and drivers of relapse in patients with schizophrenia: a systematic literature review. *Ann Gen Psychiatry* **12**:32.

Polsky D, Doshi JA, Bauer MS, Glick HA (2006). Clinical trial-based cost-effectiveness analyses of antipsychotic use. *Am J Psychiatry* **163**: 2047–2056.

Rosenheck RA, Krystal JH, Lew R, Barnett PG, Fiore L, Valley D, Liang MH (2011). Long-acting risperidone and oral antipsychotics in unstable schizophrenia. *N Engl J Med* **364**:842–851.

Sheehan JJ, Reilly KR, Fu DJ, Alphs L (2012). Comparison of the peak-to-trough fluctuation in plasma concentration of long-acting injectable antipsychotics and their oral equivalents. *Innov Clin Neurosci* **9**:17–23.

Spina E, Cavallaro R (2007). The pharmacology and safety of paliperidone extended-release in the treatment of schizophrenia. *Expert Opin Drug Saf* **6**:651–662.

Taylor D, Cornelius V (2010). Risperidone long-acting injection: factors associated with changes in bed stay and hospitalisation in a 3-year naturalistic follow-up. *J Psychopharmacol* **24**:995–999.

Taylor D, Olofinjana O (2014). Long-acting paliperidone palmitate–interim results of an observational study of its effect on hospitalization. *Int Clin Psychopharmacol* **29**:229–234.

Taylor M, Currie A, Lloyd K, Price M, Peperell K (2008). Impact of risperidone long acting injection on resource utilization in psychiatric secondary care. *J Psychopharmacol* **22**:128–131.

Wing JK, Beevor AS, Curtis RH, Park SB, Hadden S, Burns A (1998). Health of the Nation Outcome Scales (HoNOS). Research and development. *Br J Psychiatry* **172**:11–18.

Young CL, Taylor DM (2006). Health resource utilization associated with switching to risperidone long-acting injection. *Acta Psychiatr Scand* **114**:14–20.