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Health-Care Utilisation and Costs of Transition from Paliperidone Palmitate 1-Monthly to 3-Monthly Treatment for Schizophrenia: A Real-World, Retrospective, 24-Month Mirror-Image Study

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Introduction: Poor adherence to antipsychotics in patients with schizophrenia is a leading cause of relapse and functional deterioration. Long-acting injectable paliperidone may reduce relapse risks, health-care utilisation, and health-care costs in these patients.

Methods: In this 24-month mirror-image study, we compared health-care utilization and costs before and after the initiation of paliperidone palmitate 3-monthly (PP3M) treatment in patients with schizophrenia spectrum disorders. Before the initiation of PP3M, the patients received paliperidone 1-monthly (PP1M) treatment. The primary study outcomes were changes in health-care utilisation and costs over the study period.

Results: This study included 34 patients with schizophrenia spectrum disorders. During the 12-months period after the initiation of PP3M treatment, the mean duration of hospitalisation decreased from 57.7 to 28.5 days ($p = 0.03$). Moreover, significant reductions were noted in emergency room visits (PP1M vs PP3M: 0.3 vs 0.0, respectively; $p = 0.05$) and health-care costs (PP1M vs PP3M: 107,328.8 vs 57,848.6, respectively; $p = 0.03$).

Conclusion: PP3M may significantly reduce hospitalisation duration, emergency room visits, and health-care costs in patients with schizophrenia.

Keywords: schizophrenia, long-acting injectable antipsychotics, paliperidone palmitate, health-care cost, health-care utilisation

Introduction

Schizophrenia is a debilitating and disabling mental illness that affects approximately 24 million people worldwide.[1] It is not only one of the top 20 leading causes of disability globally but also a substantial contributor to the burden of mental illnesses.[2,3] Relapse in patients with schizophrenia increases health-care utilisation and costs, particularly because frequent emergency room visits and hospitalisations are often required.[4,5,6]

Antipsychotic medications are the mainstay therapy for managing schizophrenia.[7] Adherence to antipsychotic medications is crucial for improving schizophrenic symptoms, managing acute psychotic episodes, and reducing the occurrence of relapses and recurrent hospitalisations. However, >50% of all patients with schizophrenia using oral antipsychotics intermittently struggle against adherence to their daily regimen in real-world settings due to lack of illness

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insight and poor medication adherence.[8,9] Thus, long-acting injectable antipsychotics (LAIs) have emerged as an ideal pharmacotherapeutic regimen for patients with schizophrenia, particularly those with poor or no adherence to oral antipsychotics, because LAIs can be less frequently administered, indicating fewer opportunities for missing dose.[10,11,12] Paliperidone palmitate is a second-generation LAI formulation of risperidone's active metabolite. Paliperidone palmitate 1-monthly (PP1M, INVEGA SUSTENNA®) treatment was initially approved in 2009 for maintenance treatment of schizophrenia (total dose: 12 administrations per year).[13] Conversely, paliperidone palmitate 3-monthly (PP3M, INVEGA TRINZA®) treatment has been marketed since 2015 for treatment of schizophrenia in patients who have been adequately stabilised with PP1M for at least 4 months.[14]

Real-world evidence indicates that PP3M improves clinical outcomes,[15,16,17,18,19] and reduces health-care utilisation[20,21,22,23,24,25] and costs[20,21,22,23,24,25,26,27,28] in patients with schizophrenia. However, very few studies have investigated the association of PP3M use with schizophrenia in the Asia population,[19,20] indicating a need for further research. Moreover, although several studies have focused on the cost-effectiveness of PP3M,[20,22,23,24,25,26,27,28] limited data are available regarding the health-care costs of transitioning from PP1M to PP3M in this population.

The current study evaluated whether a transition from PP1M to PP3M can reduce health-care utilisation and costs in real-world patients with schizophrenia. The primary study outcomes were changes in health-care utlilisation and costs at 12 months after the initiation of the PP3M treatment.

Methods

Study Design

In this retrospective 24-month mirror-image study, we compared health-care utilisation and health-care costs before and after PP3M use in patients with schizophrenia. For all patients, the date of PP3M initiation was regarded as the mirror point (the index date). The patients received PP1M for at least 12-months before the initiation of PP3M treatment. After switching, they received PP3M treatment for the subsequent 12-month period.

This study included patients who had received a diagnosis of schizophrenia spectrum disorders (the *International Classification of Diseases, Tenth Revision, Clinical Modification* codes F20 and F25) by their psychiatrist at the Psychiatric Outpatient Department of Dalin Tzu Chi Hospital, Taiwan, and had been advised to switch from PP1M to PP3M between December 2021 and October 2023. We exclude patients aged <18 years or >75 years and those lacking complete outpatient data for at least 12 months before and after the initiation of PP3M. All patients received care as usual and PP3M was prescribed following an independent clinical decision.

Data Collection

Relevant data were collected from the patients' electronic medical records. The data included information on the patients' demographic characteristics, physical comorbidities, medication use, adverse drug reactions (ADRs), health-care costs, health care utilisation (including utilisation rates of outpatient department visits, emergency room visits, and psychiatric hospitalisation), and other medical data. Health-care costs were calculated as the sum of pharmacy and medical costs; medical costs included the costs of outpatient visits, emergency room visits, hospitalisation, home visits, and other services.[27] Moreover, the hospitalisation was defined as psychiatric hospitalisation in the study. The collected data were anonymised and stored in a secure database. All files were protected using passwords.

Statistical Analysis

The patients' baseline clinicodemographic characteristics were summarised using descriptive statistics. Categorical data are presented in terms of number and percentage values, whereas continuous data are presented in terms of mean and standard deviation value. Continuous data were subjected the Shapiro–Wilk test to determine whether they were normally distributed; the data did not exhibit a normal distribution. Thus, the Wilcoxon signed-rank and bootstrap paired *t*-tests were used for data analysis. Significance was set at $p < 0.05$. All analyses were performed using SPSS (version 22.0; IBM Corporation, Armonk, NY, USA) for Windows.

Results

Clinicodemographic Characteristics

We identified 37 patients with schizophrenia spectrum disorders who had been prescribed a transition from PP1M to PP3M during the study period. Three patients were excluded from this study for following reasons. One was hospitalised because of relapse after PP3M treatment in the first quarter; another rejected PP3M treatment in the third quarter because of ADRs such as dizziness, fatigue, and general weakness for approximately 1 week after PP3M use; and the other stopped PP3M treatment in the fourth quarter because his mother was excessively concerned about poor disease control with this formulation. Finally, this study included 34 (91.9%) patients who had used PP3M for at least 12 months.

The patients' baseline clinicodemographic characteristics are summarised in Table 1. Their mean age was 46.5 ± 10.8 years. Of the patients, 58.8% were men, 61.8% were single, and 82.4% were unemployed. The predominant diagnosis was schizophrenia (88.2%), followed by schizoaffective disorder (11.8%). The mean duration of diagnosis was 13.0 ± 6.6 years. Approximately 50.0% of the patients had physical comorbidities, such as hypertension (n = 9), diabetes mellitus (n = 8), and hyperlipidemia (n = 5). In addition to PP1M and PP3M treatments, 91.2% had concomitant oral psychiatric medications which the most common medications followed by antipsychotics (n = 17), benzodiazepine (n = 15), and mood stabilisers (n = 8). Approximately 91.2% of our patients had no ADR after PP3M use; 8.8% developed the

Table 1 Baseline Clinicodemographic Characteristics of Study Subjects (n = 34)

Characteristic	
Age, years	
Mean ± SD	46.5 ± 10.8
Range	29~72
Sex, n (%)	
Male	20 (58.8)
Female	14 (41.2)
Marital status, n (%)	
Single	21 (61.8)
Married	10 (29.4)
Others	3 (8.8)
Employed status, n (%)	
Unemployed	28 (82.4)
Employed	6 (17.6)
Diagnosis	
Schizophrenia	30 (88.2)
Schizoaffective disorder	4 (11.8)
Duration of this diagnosis, years	
Mean ± SD	13.0 ± 6.6
Range	2~22

(*Continued*)

Table 1 (Continued).

Characteristic	
Physical comorbidities, n (%)	
None	17 (50.0)
One or more than	17 (50.0)
Hypertension	9
Diabetes Mellitus	8
Hyperlipidemia	5
Osteoarthritis	3
Concomitant oral psychiatric medications, n (%)	
None	3 (8.8)
One or more than	31 (91.2)
Antipsychotics	17
Benzodiazepines	15
Mood stabilisers	8
Antidepressants	6
ADR, n (%)	
No	31 (91.2)
Yes	3 (8.8)

Abbreviations: SD, standard deviation; ADR, adverse drug reaction.

following ADRs: an injection site reaction with pain and swelling (n = 1; the reaction resolved within 3 days), tiredness persisting for 1 day after PP3M use (n = 1), and poor diabetes control leading to the use of an increased dosage of antidiabetic medications (n = 1).

Results of Outcome Analysis

Table 2 presents the health-care utilisation and costs at 12 months before and after the initiation of PP3M treatment. The mean durations of hospitalisation at 12 months before and after the initiation of PP3M treatment were 53.6 ± 93.9 and 28.5 ± 69.8 days, respectively (p = 0.02). The health-care costs at 12 months before and after the initiation of PP3M treatment were 107,328.8 ± 175,121.2 and 57,848.6 ± 132,797.2, respectively (p = 0.03). The mean numbers of emergency room visit at 12 months before and after the initiation of PP3M treatment were 0.3 and 0.0, respectively (p = 0.05). The mean numbers of outpatient department visits and psychiatric hospitalisations decreased nonsignificantly after the initiation of PP3M treatment.

Discussion

We explored the health-care utilisation and costs associated with transitioning from PP1M to PP3M treatment over a 24-month period in real-world patients with schizophrenia. The overall experience of these patients indicated significant reductions in emergency room visit risks, hospitalisation, and health-care costs. Notably, the duration of hospitalisation was reduced by >25 days. Health-care costs decreased from NT$107,328.8 for PP1M treatment to NT$57,848.6 for PP3M treatment, resulting in savings of approximately 46%.

Table 2 Health-Care Utilisation and Costs at 12 Months Before and After the Initiation of PP3M Treatment (n = 34)

	Pre-Injection PP3M		Post-Injection PP3M		Wilcoxon Signed-Rank test	Bootstrap Paired *t*-test
	Mean ± SD	Range	Mean ± SD	Range		
Number of OPD	11.7 ± 4.1	3~20	10.3 ± 4.9	4~29	0.05	0.10
Number of ER	0.3 ± 0.6	0~2	0.0 ± 0.0	0~0	0.02	0.05
Number of PH	0.8 ± 1.3	0~5	0.6 ± 1.4	0~5	0.27	0.29
Duration of Hospitalisation, days	53.6 ± 93.9	0~362	28.5 ± 69.8	0~251	0.03	0.02
Health-Care Cost, $NT dollars	107,328.8 ± 175,121.2	0~634,213	57,848.6 ± 132,797.2	0~484,286	0.03	0.03

Abbreviations: PP3M, three-monthly paliperidone palmitate; OPD, outpatient department visits; ER, emergency room visits; PH, psychiatric hospitalization; $NT dollars, new Taiwan dollars; SD, standard deviate.

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Safety and Acceptance of Transition from PP1M to PP3M

Our findings regarding patient safety (91.2%) and acceptance (91.3%) align with those of a survey on switching from PP1M to PP3M.[18] In the aforementioned study, Barnett and Pappa[18] observed high levels of safety (93.5%) and acceptance (89.2%) over 12 months of PP3M treatment in 46 patients with schizophrenia. Moreover, large-scale studies have corroborated that the safety and acceptance of PP3M treatment are similar to those of PP1M treatment in real-world settings.[15,19,29,30] Taken together, these findings indicate that as maintenance therapy for schizophrenia, PP3M treatment is associated with high safety and acceptance levels.

Health-Care Utilisation for Transition from PP1M to PP3M

The prevalence of mental illnesses is high among patients with recurrent emergency room visits, with schizophrenia-related problems being the third most frequent reason for such visits.[30] Consequently, schizophrenia-related visits often impose a considerable financial burden on the health-care system. We found that PP3M reduced the frequency of emergency room visits in patients with schizophrenia, which is consistent with findings reported in the literature.[20,21,24,25] Therefore, PP3M treatment may be an ideal pharmacotherapeutic regimen for patients with schizophrenia. Although we cannot further explain the underlying causes of the aforementioned visits, the association of a reduced frequency of emergency room visits with PP3M treatment is relevant for controlling emergency room overcrowding and alleviating financial pressure on health-care systems.[31,32]

In addition to emergency room visits, both the frequency and duration of hospitalisation can contribute to health-care costs. PP3M treatment has been demonstrated to significantly reduce the frequency of hospitalisations in many developed countries.[21,23,24,25,33] Similarly, in the current study, we noted that patients with schizophrenia who transitioned from PP1M to PP3M experienced a nonsignificant reduction in the frequency of hospitalisation. Regarding the duration of hospitalisation, a study conducted among US veterans with schizophrenia revealed a 47.8% reduction in the duration of hospitalisation at 6 months after transition from PP1M to PP3M.[23]The other six-year mirror image study showed that mean duration of hospitalisation per year 3 years before and 3 years after PP3M initiation for patients with schizophrenia significantly decreased.[33] These findings are consistent with our data, which indicate that patients with schizophrenia who switched from PP1M to PP3M within a 24-month period had 46.8% (> 25 days) reduction in the duration of hospitalisation. Collectively, these findings suggest that patients with schizophrenia undergoing PP3M treatment are likely to have improved symptom control, fewer relapses and decompensations, functional remission, and enhanced quality of life.

Health-Care Costs for Transition from PP1M to PP3M

Recent evidence indirectly indicates that PP3M reduces health-care costs by reducing hospitalisations and emergency room visits.[20,22,26,27,28] However, few studies have directly calculated health-care costs during the transition from PP1M to PP3M treatment.[23,24,25,33] The Spanish National Health System reported that the expected health-care cost of PP3M (€4780) was lower than that of PP1M (€5244) in patients with chronic schizophrenia, indicating a total of health-care cost reduction of 8.8%.[24] Similarly, a study in the Netherlands revealed that the expected cost for chronic schizophrenia treatment was lower for PP3M (€8781) than for PP1M (€10,325), indicating cost-saving of approximately 15.5%.[25] Furthermore, US veterans with schizophrenia who appropriately transitioned from PP1M to PP3M treatment were reported to benefit from reduced health-care costs, with savings reported of approximately 14.3%.[23] In the current study, we discovered that the health-care cost was 46% lower for patients with schizophrenia undergoing PP3M treatment than for those undergoing PP1M treatment. Overall, given that PP3M substantially reduces health-care costs, it may be a better pharmacotherapeutic regimen for patients with schizophrenia, particularly those with no or poor treatment adherence.

Although this study did not further evaluate the pharmacokinetic difference between PP1M and PP3M, the difference may affect the choice of medication prescription. For example, prolactin levels and potentially sexual adverse effects for switching from PP1M to PP3M significantly decreased despite the difficult formulations of the same drug.[34] The sexual

adverse effects between PP1M and PP3M may affect the choice of medication prescription in clinic, especially in high-functioning marriageable-age patients with schizophrenia.

Strengths and Limitations of the Study

A key strength of this observational, mirror-image study is the naturalistic, nonrandomised, open evaluation of clinical outcomes and health-care costs in a real-world clinical setting. Another strength lies in the fact that the study design allowed for the patients and physicians to serve as their own controls.

The study has several limitations. First, it lacked a contemporaneous comparator, which increases the difficulty of assessing the relative treatment efficacy. Second, the possibilities of biases such as temporal and selection biases cannot be ignored. In terms of selection biases, we included the patients who were previously stabilised and responded to PP1M and therefore effectively excluded those who had not responded or tolerated PP1M in the study. In addition, one might anticipate that PP1M responders will have a positive response and better outcome with PP3M. The cohort comprised only outpatients who had been prescribed a transition from PP1M to PP3M at least 24 months before the initiation of the present study. Third, we could not further assess reasons for switching from PP1M to PP3M in each case with schizophrenia. We only recorded PP3M prescription following an independent clinical decision, although several reasons need to be considered in each case with schizophrenia, including convenience, health satisfaction, improved quality of life, a decrease in carer burden, decreased stigma and better adherence.[18,35,36,37] Finally, we relied on indirect data for evaluating clinical outcomes, that is, the number of emergency room visits and the duration of hospitalisation.

Conclusion

Our real-world data indicate that a transition from PP1M to PP3M can significantly reduce hospitalisation duration, emergency room visits, and health-care costs in patients with schizophrenia. In the future, large-scale studies should be conducted to validate our findings.

Data Sharing Statement

The data underlying this article will be shared upon reasonable request to the corresponding author.

Ethics Approval

This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review board of Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chiayi, Taiwan (IRB No.: B11204003). The patient consent was not required because of de-identification ensures that any medical records are unable to be tracked down to any individual patients in this study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest related to the current work.

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