Neuropsychiatric Disease and Treatment

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REVIEW

Paliperidone Palmitate: A Breakthrough Treatment for Schizophrenia? A Review on Patient Adherence Levels, Healthcare Resource Utilization and Costs

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Abstract: International guidelines suggest long-term antipsychotic therapies for treating schizophrenia; however, medication compliance remains a critical issue in schizophrenia. Paliperidone palmitate (PP) is a second-generation antipsychotic long-acting injectable (SGA-LAI) approved for the treatment of schizophrenia. To date, the majority of studies on PP compliance patterns did not use specific instruments to assess medications' adherence, have been performed in not naturalistic samples and present partially overlapping populations. We conducted a systematic review in which we aimed to review the current knowledge on PP-LAI adherence levels and to describe healthcare resource utilisation and costs related to PP-LAI treatment. The evaluation has been conducted by searching in different databases (PubMed, Ovid, Scopus, and Cochrane Library) from inception to September 2022. Our findings suggest that paliperidone palmitate should be considered a good treatment strategy for patients affected by schizophrenia: PP showed both a good efficacy and tolerability and better adherence patterns and more favourable healthcare resource utilisation and costs, compared to OA.

Keywords: compliance, long-acting injectables, oral antipsychotics, schizophrenia

Introduction

International guidelines suggest long-term antipsychotic therapies for treating schizophrenia, given its proven effect to improve clinical and non-clinical outcomes, in all stages of the disorder.[1]

Despite the need for continuous drugs treatment, medication compliance remains a critical issue in schizophrenia, with non-adherence rates ranging from 34% to 81%.[2–8] Antipsychotics non-adherence leads to a greater risk of relapses and negative overall outcomes.[9,10] Several factors, such as lack of insight, comorbid disorders (substances use and depressive symptoms), side effects, cognitive impairment and high hostility levels, can play a role in medication non-adherence in schizophrenia.[11] Over the years different approaches have been proposed to improve adherence, such as psycho-education, cognitive-behavioural techniques, motivational interviewing, financial incentives and new pharmacological formulations.[1,12]

Several studies showed clinical and economics advantages of long-acting injectables (LAI) compared to oral antipsychotics (OA),[13–15] with a higher clinical effectiveness and better tolerability, due to a greater compliance,[16–19] the more stable blood levels and the specific modality of administration.[20] As a consequence, different authors suggest LAI for both individuals with a high non-adherence risk and also for early stages of schizophrenia.[1,21,22]

Paliperidone palmitate (PP) is a second-generation antipsychotic LAI (SGA-LAI) approved for the treatment of schizophrenia. To date, there are three different PP-LAI formulations: paliperidone palmitate once-monthly (PP1M), paliperidone palmitate 3-monthly (PP3M) and paliperidone palmitate 6-monthly (PP6M). All the three formulations

Received: 9 December 2022
Accepted: 22 February 2023
Published: 7 March 2023

showed good efficacy, safety and tolerability for the treatment of subjects with Schizophrenia.[23–25] However, less attention has been paid to PP-LAI adherence levels versus OA. To date, the majority of studies on PP-LAI compliance patterns did not use specific instrument to assess medications' adherence, have been performed in not naturalistic samples and present partially overlapping populations. The Pharmacy Quality Alliance encourages the use of the proportion of days covered (PDC) – number of days covered by the medication divided by the number of days of the specific period of observation – as the best method to evaluate medications' compliance. However, only a minority of papers use this parameter to study adherence patterns in subjects treated with PP. Moreover, increased adherence levels related to LAI therapies are associated with several non-clinical outcomes, such as healthcare resource utilisation (HRU) and healthcare costs (HC),[15] but data on HRU and HC from the studies on PP have not been systematized yet.

The primary aim of this review is to present the current knowledge on PP-LAI adherence levels. The secondary aim is to describe healthcare resource utilization and healthcare costs related to PP-LAI treatment, in those studies in which adherence patterns have been evaluated.

Materials and Methods

The systematic review was conducted using the PRISMA guidelines.[26,27]

The studies were retained if they met the following criteria: a) included subjects affected by schizophrenia and treated with PP, b) conducted in real-world setting with adherence patterns as an endpoint of interest, c) adherence evaluated only in cohort studies (individuals receiving PP vs individuals treated with OA) or mirror studies (among the same patients, before and after PP initiation) d) adherence analysed using the PDC method. Selected papers have also been evaluated in order to analyse HRU and HC related to PP treatment.

The evaluation has been conducted by searching in different databases (PubMed, Ovid, Scopus, and Cochrane Library) from inception to September 2022. The terms "adherence" and "compliance" were associated using the boolean AND with "paliperidone palmitate" and "long-acting injectables antipsychotics". Moreover, a manual search for possible eligible articles from papers previously selected or from other reviews/meta analysis on this topic was conducted. We limited our research to English-language reports.

A three steps evaluation's process has been conducted by three Authors (GR, GDS and SB): title, abstract and full text. The studies included were independently chosen by each Author, according to inclusion criteria and clinical significance. The senior Reviewer (GM) has been consulted in case of disagreement between Authors.

Results

Figure 1 reports a flowchart of all papers evaluated and included in this review. Ten studies were selected: nine retrospective cohort studies[28–36] and one mirror study.[37] Among these papers, two studies showed data on adherence patterns only[29,34] and eight studies presented data on adherence levels and other clinical outcomes.[28,30–33,35–37] Moreover, compliance patterns have been studied in subjects receiving exclusively PP1M in eight papers,[28–30,33,34,36,37] while two studies reported data on a population treated with different LAI, including PP1M.[32,35] Finally, in all the studies, patients were treated with PP1M; no data on PP3M and PP6M were found (Table 1).

Adherence

Using the PDC, adherence to treatment has been expressed in different ways: PDC mean values; proportion of good treatment adherence (defined as a PDC≥80%), and odds of having a good adherence. Only one paper evaluated predictors of adherence.[28]

The first published paper selected aimed to compare typical measures of compliance (PDC) between patients with schizophrenia treated with LAI and OA.[29] The Authors evaluated 195 subjects who initiated PP1M and 369 individuals receiving oral aripiprazole, from August 2009 to April 2010. In this retrospective cohort study, PDC values were significantly higher in the population treated with PP1M compared to the patients treated with OA. Considering the specificity of LAI formulation's, the Authors evaluated PP1M compliance using four different approaches (Data as Received; Derived Days=30 days, Derived Days=28 days and Covered Days), in order to minimize the risk of over-

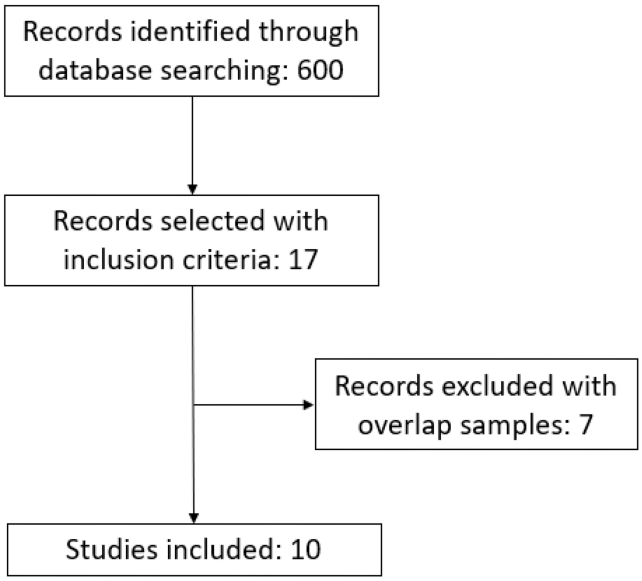

Figure 1 Flow diagram of the systematic review.

inflation of the days' supply field and overestimation of adherence, when early LAI administrations are performed. PDC mean values were significantly higher in the LAI group (Data as Received = 0.59, p = 0.003; Derived Days-30 days = 0.61, p < 0.001; Derived Days-28 days = 0.58, p < 0.001 and Covered Days = 0.55 p = 0.0039) compared to OA (0.37) in the year following drug initiation. A higher proportion of PDC≥80% was also observed in the PP1M group (Data as Received = 36.4%, p = 0.005; Derived Days-30 days = 37.9%, p = 0.002; Derived Days-28 days = 35.4%, p = 0.011) compared to the OA cohort (25.2%).

Two years later, Young-Xu et al[31] analysed electronic medical health record data from the Veterans Health Administration of subjects treated with PP1M or OA between January 2010 and October 2014. Adherence levels were evaluated during the 12-month study period, after the index medication initiation. The OA analysed in this study were aripiprazole, asenapine, iloperidone, lurasidone, olanzapine, quetiapine, risperidone, ziprasidone and oral paliperidone. After applying the inverse probability of treatment weights, two treatment cohorts were generated: 5052 PP1M patients and 5238 OA subjects. PP1M individuals showed higher rates of good treatment adherence (PDC ≥ 80%) compared to OA users (35.8% vs 23.3%; p < 0.001).

In 2017 four research groups compared medication adherence using PDC, between subjects treated with PP1M versus individuals receiving OA. Among them, two studies reported data on a population treated with several LAIs (PP1M included),[32,35] while the others were exclusively focused on PP1M.[28,33]

Greene et al[32] performed two different analyses in order to evaluate treatment patterns in patients affected by schizophrenia and bipolar disorder, using the Truven Health Analytics MarketScan Multi-State Medicaid claims database (January 2012-June 2015). Adherence has been studied between individuals who started an LAI and subjects who switched from an OA to another OA, during the 12-month observation period. The group of patients with schizophrenia consisted of 2861 LAI users (50.7%) (aripiprazole monohydrate, fluphenazine decanoate, haloperidol decanoate, olanzapine pamoate, paliperidone palmitate, risperidone microspheres) and 2777 OA users (49.3%) (quetiapine, risperidone, olanzapine, lurasidone, aripiprazole, ziprasidone, haloperidol, paliperidone and other). The LAI group had higher medication adherence: before adjustment PDC mean values were 0.55 vs 0.50 (p < 0.001) and rates of good treatment adherence (PDC ≥ 80%) were 33.9% vs 25.5% (p < 0.001). After controlling for all differences in measured covariates, PDC mean values remained significantly higher (p < 0.001) in the first group (0.55) compared to the second group (0.50).

Pilon et al conducted a retrospective cohort study,[35] in which Medicaid data of 3307 patients receiving LAI (paliperidone palmitate, aripiprazole, risperidone and olanzapine) were compared to data of 21,355 subjects treated with atypical OA (aripiprazole, asenapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone and

Table 1 Differences Between Adherence Patterns Among Patients Treated with Paliperidone Palmitate and Oral Antipsychotics: Results from Observational Studies, Using PDC as a Measure of Compliance

Authors	Study Design	Sample (N)	Treatment	Adherence	
Campagna et al, 2014[29]	Retrospective Cohort Study	LAI: 195 OA: 369	PP1M Aripiprazole	**PDC mean** PP1M: • Data as received: 0.59 • Derived Days-30 days: 0.61 • Derived Days −28 days: 0.58 • Covered Days: 0.55 OA: 0.37 **PDC ≥80%** PP1M: • Data as received: 36.4% • Derived Days-30:37.9% • Derived Days −28:35.4% • Covered Days: 27.2% OA: 25.2%	 p=0.003 p<0.001 p<0.001 p=0.0039 p<0.005 p=0.002 p<0.011 p=0.610
Young-Xu et al, 2016[31]	Retrospective Cohort Study	LAI: 5052 OA:5238	PP1M Aripiprazolo, Asenapine, Iloperidone, Lurasidone, Olanzapine, Quetiapine, Risperidone, Ziprasidone Paliperidone.	**PDC≥ 80%** PP1M: 35.8% OA: 23.3%	 p<0.001
Greene et al, 2018[32]	Retrospective Cohort Study	LAI: 2861 OA: 2777	Aripiprazole Monohydrate, Fluphenazine Decanoate, Haloperidol Decanoate, Olanzapine Pamoate, PP1M, Risperidone Microspheres. Quetiapine, Risperidone, Olanzapine, Lurasidone, Aripiprazole, Ziprasidone, Haloperidol, Paliperidone.	**PDC mean** PP1M: 0.55 OA: 0.50 **PDC≥80%** PP1M: 33.9% OA: 25.5%	 p<0.001 p<0.001
Pilon et al, 2017[35]	Retrospective Cohort Study	LAI: 3307 OA: 21,355	PP1M, Aripiprazole, Risperidone, Olanzapine. Aripiprazole, Asenapine, Iloperidone, Lurasidone, Olanzapine, Paliperidone, Quetiapine, Risperidone, Ziprasidone.	**PDC mean** PP1M: 0.55 OA: 0.53 **PDC≥80%** PP1M: 31.1% OA: 28.1%	 p<0.001 p<0.001
Pesa et al, 2017[33]	Retrospective Cohort Study	LAI: 1939 OA: 3786	PP1M Aripiprazole, Asenapine, Iloperidone, Lurasidone, Olanzapine, Paliperidone	**PDC mean** PP1M: 0.7 OA: 0.6	 p<0.001
Anderson et al, 2017[28]	Retrospective Cohort Study	LAI: 482 OA: 281	PP1M Atypical Antipsychotics	**PDC mean** PP-N+PP-C: 0.57 OA: 0.31 PP-N: 0.53 OA: 0.31 **PDC ≥80%** PP-N+PP-C: 44% OA: 9% PP-N: 39% OA: 9% **Predictors of PDC ≥80%** PP1M initiation: OR 10.3 PP1M continuation: OR 16.5 Older age: OR 1.3 History of arrest: OR 4.2 Private residence OR 1.9 White race OR 2.5 Heart Disease OR 3.4 No history of substance abuse OR 2.3	 p<0.001 p<0.001 p<0.001 p<0.001 p<0.001 p<0.001 p=0.028 p=0.031 p=0.012 p<0.001 p=0.010 p<0.001

(*Continued*)

Table 1 (Continued).

Authors	Study Design	Sample (N)	Treatment	Adherence	
Joshi et al, 2018[36]	Retrospective Cohort Study	LAI: 295 OA: 2296	PP1M Aripiprazole, Asenapine, Iloperidone, Lurasidone Olanzapine, Paliperidone, Quetiapine, Ziprasidone	**PDC mean** PP1M: 0.66 OA: 0.57	p<0.001
El Khoury et al, 2019[37]	Mirror Study (12 months pre/post PP1M) (6 months pre/post PP1M)	− 6 months: 401 –12 months: 319	PP1M Risperidone, Paliperidone	**PDC mean** 6 months Pre PP1M: 0.4 Post PP1M: 0.6 12 months Pre PP1M: 0.3 Post PP1M: 0.5 **PDC ≥80%** 6 months Pre PP1M: 12.5% Post PP1M: 40.6% 12 months Pre PP1M: 7.2% Post PP1M: 27.6%	p<0.001 p<0.001 p=0.0007 p<0.001
Patel et al, 2021[30]	Retrospective Cohort Study	LAI: 208 OA: 624	PP1M Atypical Antipsychotics	**PDC mean** After 6 months PP1M: 0.53 OA: 0.46 After 12 months PP1M: 0.41 OA: 0.34	p=0.0013 p=0.008
Wang et al, 2021[34]	Retrospective Cohort Study	JMDC LAI: 249 OA: 40,058 PKU LAI: 428 OA: 6450 XJH LAI: 189 OA: 3884	PP1M Atypical Antipsychotics	**PDC ≥80%** JMDC PP1M: 66% OA: 52% MPKU PP1M: 36% OA:19% XJH PP1M:35% OA:15% **ODD of having PDC ≥80%** (LAI) JMDC PP1M: OR 1.61 PKU PP1M: OR 1.92 XJH PP1M: OR 2.25	p< 0.01 p< 0.01 p<0.01 p<0.01 p<0.01 p<0.01

Abbreviations: PP1M: Paliperidone Palmitate Once Monthly; OA: Oral Antipsychotic; LAI: Long Acting Injectable; PP-N: Paliperidone Palmitate-New; PP-C: Paliperidone Palmitate-Continued. PDC: Proportion of Days Covered; JMDC: Japan Medical Data Center; PKU: Peking University No.6 Hospital; XJH: Xijing Hospital.

ziprasidone), between January 2009 and March 2015. Treatment patterns were studied during the 12-month observation period. Unadjusted adherence outcomes were more favourable for the SGA-LAI group compared to the OA group: the PDC mean value was 0.55 vs 0.53 ($p < 0.001$) and the proportion of good adherence (PDC≥ 80%) was 31.1% vs 28.1% ($p < 0.001$). Moreover, these results seemed to be especially due to PP1M outcomes: the adherence patterns observed among aripiprazole and risperidone users were similar to the OA group. The PP1M individuals showed higher PDC mean values (0.57 vs 0.53, $p < 0.001$) and rates of good adherence (33.0% vs 28.1%, $p < 0.001$). After adjustment, the odds of being adherent to the therapy were 1.28 times higher for the SGA-LAI group ($p < 0.001$) and this seemed mainly driven by the PP1M group data again (OR 1.39, $p < 0.001$).

In the retrospective cohort study by Pesa et al[33] the Medi-Cal database data of 5725 patients were analyzed (from July 2008 to December 2014). The PP1M cohort had 1939 patients and the OA cohort had 3786 individuals. Each subject in the PP1M group was matched 1:1 to an individual in the OA group (aripiprazole, asenapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone), using greedy match method and controlling for some covariates. As a consequence, 722 patients were selected for both the PP1M cohort and the OA cohort. During the 12-month follow-up period the PP1M group had significant higher PDC mean values compared to the other group (0.7 vs 0.6, $p < 0.001$).

Anderson et al[28] performed a retrospective cohort evaluation of 763 subjects of the REACH-OUT study (2010–2013) treated with PP1M (482 patients) or atypical OA (281 patients). Among the PP1M users, at enrollment 174 individuals were initiating a new therapy with PP (PP-N), while 308 subjects continued the previously started PP treatment (PP-C). At one year, all PP users (PP-N plus PP-C) had higher PDC mean values compared to OA users (0.57 vs 0.31, $p < 0.001$) and PP-N users showed higher PDC mean values compared to OA users (0.53 vs 0.31, $p < 0.001$). Rates of good adherence (PDC≥ 80%) were significantly higher both in the PP-All cohort and in the PP-N cohort compared to the OA cohort (44% vs 9%, $p < 0.001$) (39% vs 9%, $p < 0.001$). Moreover, the Authors found several variables as predictors of good treatment. PP1M initiation and continuation resulted in an increased likelihood of good adherence (OR 10.3, $p < 0.001$; OR 16.5, $p < 0.001$), as well as older age (OR 1.3, $p = 0.028$) history of arrests (OR 4.2, $p = 0.031$), private residence (OR 1.9, $p = 0.012$), white race (OR 2.5, $p = 0.001$), heart disease (OR 3.4, $p = 0.010$) and no history of substance abuse (OR 2.3, $p = 0.001$).

In 2018, Joshi et al[36] retrospectively analysed data of 2591 patients of the Humana Research Database (January 2009–September 2015). Two cohort were identified: 295 PP1M individuals and 2296 OA individuals. The OA studied were: aripiprazole, asenapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine or ziprasidone. In order to reduce baseline differences between the groups, the Authors used the inverse probability of treatment weights (IPTW) method, resulting in weighted number of observations in each IPTW pseudo-cohort (1087 PP1M weighted and 1190 OA weighted). At 12 months adherence patterns of the LAI group were better than the OA cohort: PDC mean values were 0.66 for the first group and 0.57 for the second group ($p < 0.001$), as well as the rates of good adherence (PDC ≥ 80%) (48.1% vs 32.6%, $p < 0.001$). Moreover, compared to the PP1M cohort, the overall antipsychotic class (not only the index medication) showed overlapping PDC data (PDC mean values: 0.77 vs 0.70, $p < 0.001$) (PDC ≥ 80%: 65.9% vs 49.3%, $p < 0.001$).

The only mirror study evaluated in this narrative review reports data on patients with schizophrenia pre and post PP1M initiation.[37] Using the Veterans Health Administration database, the Authors studied treatment patterns among subjects who switched from a previous treatment with oral risperidone/paliperidone to PP1M (January 2014 – March 2018). Adherence levels of the 12-months pre and post transition to PP1M (319 individuals) and 6-months pre and post transition to PP1M (401 individuals) were reported. PDC mean values of OA 6-months pre-transition were 0.4, while PDM mean values post PP1M transition were 0.6 ($p < 0.001$). Rates of adherence (PDC≥ 80%) were also higher after LAI initiation compared to risperidone/paliperidone treatment (40.6% vs 12.5%, $p = 0.0007$). During the year before transition to PP1M, PDC mean values for risperidone/paliperidone were 0.3 and rates of adherence were 7.2%. At 12-months post PP1M transition, PDC mean values were 0.5 ($p < 0.001$) and rates of adherence were 27.6% ($p < 0.001$).

Recently, Patel et al[30] analysed Medicaid data (2009–2018) of patients affected by schizophrenia, treated with PP1M or atypical OA within 30 days after the first relapse of the disorder (emergency/inpatient evaluation related to schizophrenia). The sample consisted of 208 individuals in the PP1M group and 3679 individuals in the OA group. The first cohort was matched 1:3 to subjects in the OA group based on exact matching factors and propensity scores obtained from a logistic regression model, resulting in 208 patients in the PP1M cohort and 624 patients in the OA cohort. Compliance has been evaluated at 6 months and 12 months post-index medication date. PDC mean values were higher in the PP1M cohort (52.6) at 6 months compared to the OA cohort (46.2) ($p = 0.013$); similar results were found at 12 months (41.2 vs 34.7, $p = 0.008$).

Finally, in a retrospective cohort study, Wang et al[34] confronted patients treated with PP1M and second generation oral antipsychotics (SGOA) in China and Japan (2012–2017). Data were obtained from the Peking University (PKU)

(tertiary mental health center) and the Xijing Hospital (XJH) (tertiary general hospital) in China and from the JDMC database in Japan. All patients were evaluated after 1 year of observation. The proportion of good compliance (PDC≥ 80%) was higher in the PP1M cohort than the SGOA cohort in all databases (JMDC: 66% vs 52%; PKU: 36% vs 19%; XJH: 35% vs 15%). Moreover, the adjusted odds of having a good adherence were significantly higher in the PP1M group compared the SGOA group (JMDC: OR 1.61, $p < 0.01$; PKU: OR 1.92, $p < 0.01$; XJH: 2.25, $p < 0.01$).

Other Clinical Outcomes

In the aforementioned studies evaluating adherence patterns of patients treated with PP1M, among other significant clinical outcomes, we focused on healthcare resource utilisation (HRU) and healthcare costs (HC).

Healthcare Resource Utilisation

Young-Xu et al[31] found less frequent all-cause inpatient hospitalisations in the PP1M group compared to the OA cohort: lower rates of inpatient stays (IRR = 0.89, $p < 0.001$) and days in an inpatient setting (IRR = 0.82, $p < 0.001$). Similar data were also available for the mental health stays (IRR = 0.92, $p < 0.001$; IRR = 0.88, $p < 0.001$), long-term care stays (IRR = 0.62, $p < 0.001$; IRR = 0.59, $p < 0.001$) and other inpatient stays (IRR = 0.84, $p < 0.001$; IRR = 0.63, $p < 0.001$). Moreover, they found increased rates of outpatient visits (IRR = 1.03, $p < 0.001$), mental health intensive case management visits (IRR = 1.81, $p < 0.001$) and reduced other outpatient visits (IRR = 0.89, $p < 0.001$) in the PP1M group. The number of subjects with a mental health inpatient stay was higher in the OA group compared to the PP1M group (82.8% vs 79.9%, $p < 0.001$). Moreover, after a mental health inpatient stay, the OA group showed higher rates of inpatient stay within 7 days of discharge (14.5% vs 11.8%, $p < 0.001$), both for mental health stays (12.9% vs 10.6% $p = 0.001$) and other inpatient stays (2.4% vs 1.7%, $p = 0.031$), and higher rates of inpatient stays within 30 days of discharge (29.1% vs 26.6%, =p=0.010), both for mental health stays (25.7% vs 23.2%, $p = 0.009$) and long-term care stays (0.9% vs 0.3%, $p < 0.001$). Regarding outpatient service after an inpatient stay, the OA group showed lower rates of overall outpatient visits (90.5% vs 93.3%, $p < 0.001$), mental health intensive case management visits (16.6% vs 26.8%, $p < 0.001$), but higher rates of emergency room visits (15.6% vs 12.2%, $p < 0.001$), within the 7 days of discharge. Similar results were found for the overall outpatient visits (96.1% vs 97.8%, $p < 0.001$) and mental health intensive case management visits (20.0% vs 30.8%, $p < 0.001$) within 30 days of discharge.

In 2017, the Pilon et al[35] analysis showed that the SGA group had less long-term care admissions (IRR = 0.67, $p < 0.001$), home care services (IRR = 0.75, $p < 0.001$) and other services (IRR = 0.84, $p < 0.001$), fewer long-term care days (IRR = 0.75, $p < 0.001$). On the other hand, the SGA cohort showed more mental health institute admissions (IRR = 1.16, $p < 0.001$), one-day mental health institute visits (IRR = 1.16, $p < 0.001$) and longer mental health institute days (IRR = 1.10, $p < 0.001$), compared to the OA cohort. In particular, the paliperidone palmitate group had fewer outpatient visits (IRR = 0.92, $p = 0.004$), inpatient days (IRR = 0.78, $p = 0.004$), long-term care admissions (IRR = 0.43, $p < 0.001$), long-term care admission days (IRR = 0.52, $p < 0.001$) home care services (IRR = 0.75, $p < 0.001$), and other services (IRR = 0.84, $p > 0.001$). Moreover, this cohort had higher mental health institute admissions (IRR = 1.16, $p < 0.001$), mental health institute admission days (IRR = 1.13, $p<0.001$), and one-day mental health institute visits (IRR = 1.17, $p < 0.001$). The risperidone group showed increased mental health institute admissions (IRR = 1.16, $p < 0.001$) and one-day mental health institute visits (IRR = 1.17, $p < 0.001$); on the contrary this cohort had fewer home care services (IRR = 0.76, $p = 0.012$) and other services (IRR = 0.83, $p = 0.008$). The aripiprazole group did not have significant differences compared to the OA group.

In the retrospective study by Pesa et al[33] the PP1M cohort showed fewer rates of any inpatient visits (61.6% vs 77.4%, $p < 0.001$), any outpatient emergency room visits (49.0% vs 56.0%, $p = 0.008$), or any other outpatient visits (78.8% vs 89.6%, $p < 0.001$). Moreover, PP1M individuals had fewer mean hospitalization days (15.0 vs 27.7, $p < 0.001$), mean inpatient visits (5.0 vs 7.9, $p < 0.001$), mean outpatient emergency room visits (2.1 vs 2.9, $p = 0.016$), and other outpatient visits (13.1 vs 16.2, $p = 0.004$).

Joshi et al[36] compared HRU of patients treated with PP1M and OA. The PP1M group had lower rates of all-cause outpatient visits (93.8% vs 98.4%, $p < 0.001$), of all-cause hospitalisations (34.1% vs 39.1%, $p = 0.013$), lower mean number of hospitalisations (0.62 vs 0.85, $p = 0.002$) and inpatient days (4.73 vs 7.28, $p = 0.0014$). Related to the mental

HRU, the PP1M cohort had lower rates of outpatient visits (31.8% vs 47.3%, $p < 0.001$) and fewer inpatient days (1.03 vs 1.86, $p = 0.006$). The weighted logistic regression and Poisson model showed that the PP1M group had a lower odd of all-cause of hospitalisation (OR: 0.81, $p < 0.05$), incidence rate of all-cause hospitalisations (IRR: 0.73, $p < 0.05$), lower number of mental health-related hospitalisations (IRR: 0.71, $p < 0.05$).

In the mirror study by El Khoury,[37] HRU were evaluated at 6 months and 12 months pre and post PP1M initiation. At 6 months post PP1M, all-cause number of inpatient stays and inpatient length of stay decreased (2.6 vs 0.9, $p < 0.0001$) (30.7 vs 11.0 days, $p < 0.0001$); the number of outpatient visits and pharmacy visits increased (26.8 vs 32.0, $p < 0.0001$) (13.2 vs 17.5, $p < 0.0001$). At 12 months, a shorter inpatient length of stay (43.4 vs 18.3 days, $p < 0.0001$), lower number of all-cause inpatient stays (3.5 vs 1.4, $p < 0.0001$), increased number of outpatient visits (48.9 vs 58.1, $p < 0.0001$) and increased number of pharmacy visits (25.8 vs 33.6, $p < 0.0001$) were found post PP1M initiation.

More recently, the patients in the PP1M group showed a lower odd of having ≥1 all-cause inpatient admissions (OR: 0.58, $p < 0.001$), number of inpatient admissions (OR: 0.71, $p = 0.004$) and days spent in an inpatient setting (OR: 0.63, $p = 0.004$).[30]

Healthcare Costs

Young-Xu et al[31] compared healthcare costs between the PP1M cohort and the OA cohort. Differences between groups were evaluated in the total sample and in two sub-groups of patients (patients with and without at least one mental health intensive case management visit at baseline). In the total sample, some cost differences were more favourable to PP1M compared to OA: total overall costs (-$8511.36, $p = 0.012$), total medical costs (inpatients + outpatients) (-$11,928.32, $p < 0.001$), total inpatient stay costs (-$14,455.76, $p < 0.001$), mental health stay costs (-$7414.95, $p < 0.001$) and other inpatient stay costs (-$4812.69, $p < 0.001$). Considering outpatient and pharmacy services, cost differences were less favourable to the PP1M group: total outpatient visit costs ($2527.44, $p < 0.001$), mental health intensive case management costs ($3114.10, $p < 0.001$), total pharmacy costs ($3416.96, $p < 0.001$) and outpatient pharmacy costs ($3299.58, $p < 0.001$). A similar trend was found for both patients with and without at least one mental health intensive case management visit at baseline.

In the retrospective study by Pilon et al[35] the groups of individuals taking SGA-LAI had lower medical costs (mean monthly cost differences) (-$168, $p < 0.001$) and this result was mainly driven by the PP1M-LAI group (-$225, $p < 0.001$). On the contrary, the SGA-LAI, in particular the PP1M group ($97, $p = 0.016$), showed higher total health care costs ($103, $p < 0.001$) and pharmacy costs ($271, $p < 0.001$). Pharmacy costs were significantly higher in the aripiprazole ($189, $p = 0.012$), paliperidone ($322, $p < 0.001$) and risperidone ($163, $p < 0.001$) groups compared to OA. Analysing medical costs by each category, the SGA-LAI cohort had lower emergency department visit costs (-$4, $p < 0.001$), inpatients visit costs (-$107, $p < 0.001$) and home care costs (-$100, $p < 0.001$), while the one-day mental health institute visit costs where higher ($33, $p < 0.001$), compared to the OA group. Similar findings resulted from the sub-group analysis: the PP1M group had lower emergency department visit costs (-$3, $p < 0.001$), inpatients visit costs (-$115, $p < 0.001$) long-term care admission costs (-$63, $p < 0.001$) and home care costs (-$113, $p < 0.001$). The risperidone group showed less emergency department visit costs (-$7, $p < 0.001$) and inpatient visit costs (-$101, $p < 0.001$). Both the PP1M and risperidone group had higher one-day mental health institute visit costs ($40, $p < 0.001$) ($22, $p < 0.001$), while only the risperidone cohort showed higher long-term care admission costs ($59, $p = 0.048$).

Pesa et al[33] did not find significant differences between the PP1M and OA groups related to total health care costs ($25,546 vs $25,307, $p = 0.853$). Despite the pharmacy costs were higher in the PP1M cohort ($16,347 vs $9115, $p < 0.001$), all the other parameters were more favourable for the PP1M group: lower inpatient visit costs ($5060 vs $10,880, $p < 0.001$), outpatient emergency room visit costs ($379 vs $547, $p = 0.021$), outpatient office visit costs ($997 vs $1412, $p = 0.012$), and other outpatient hospital costs ($2763 vs $3353, $p = 0.019$).

Joshi et al[36] compared healthcare costs between PP1M individuals and OA subjects: total costs ($25,882 vs $21,332, $p < 0.001$) and pharmacy costs ($14,787 vs $5781, $p < 0.001$), were significantly higher in the first group. On the contrary, the PP1M cohort had lower costs related to medical costs ($11,095 vs $15,551, $p < 0.001$), hospital costs ($4885 vs $8333, $p < 0.001$), emergency department costs ($984 vs $1281, $p<0.001$), and outpatient costs ($2501 vs $3206, $p < 0.001$).

In the mirror study by El Khoury et al[37] healthcare costs were evaluated at 6 months and 12 months pre/post PP1M transition. Inpatients stay costs ($47,829 vs $17,671, p < 0.0001), total medical costs ($59,675 vs $34,229, p < 0.0001) and total costs ($60,877 vs $41,136, p < 0.0001) were significantly lower at 6 months post PP1M initiation. Similar results were found at 12 months ($23,215 vs $30,800, p < 0.0001) ($87,917 vs $56,947, p < 0.0001) ($91,181 vs $69,106, p < 0.0001). Outpatients visit costs and pharmacy costs were significantly higher from pre to post PP1M transition at 6 months and 12 months ($11,846 vs $16,558, p < 0.0001) ($1202 vs $6906, p < 0.0001) ($23,215 vs $30,800, p < 0.0001) ($3263 vs $12,159, p < 0.0001).

Finally, in the retrospective study by Patel et al[30] mean all-cause annual medical cost differences were more favourable for the PP1M group (-$6273, p = 0.028), as well as mean cost differences related to the outpatient visits (-$745, p = 0.024). On the contrary, pharmacy costs were significantly higher in the PP1M cohort compared to the OA cohort ($9836 vs $5066, p < 0.001).

Discussion

The primary aim of this article was to review literature data on the current knowledge on PP adherence patterns.

Although a large number of studies describe the efficacy and good tolerability of PP-LAI,[25–27] there is a paucity of data on PP compliance levels. Moreover, there is a lack of specific instrument to assess medications' adherence and the majority of the researches on this topic have been performed in not real-world studies, with partially overlapping samples.

Despite the aforementioned limitations, data from naturalistic studies (cohort and mirror studies), with PDC as a measure of compliance, consistently describe significantly better adherence patterns in subjects treated with PP compared to OA. Favourable adherence outcomes related to PP have been highlighted in all the studies selected, with similar results both in Asian[34] and US populations.[28–33,35–37] PP showed higher adherence rates when compared to first-generation[32] and second-generation antipsychotics.[28–33,35–37] Even when the PP cohort was compared with the oral Paliperidone cohort,[37] the first group showed higher medication adherence, suggesting a significant role of the route (injection versus oral) and frequency of administration. Similar results were also found in subjects who received PP1M within one month the first relapse of the disorder.[30] Moreover, no differences have been found when PP has been studied as the only index medication[28–31,33,34,36,37] or with other LAI.[32,35] Noteworthy, in the retrospective study by Pilon et al[35] the LAI higher adherence patterns were mainly driven by the PP1M cohort, whereas risperidone-LAI and aripiprazole-LAI compliance levels were similar to the OA group. This finding suggests a specific PP's effect in the adherence patterns. However, direct comparisons between SGA-LAI were not performed and, as a consequence, these results should be interpreted with caution and need to be confirmed by other studies. A possible explanation is that some specific factors related to PP treatment, such as tolerability profile, could improve medication adherence. Medication side effects play a significant role for adherence patterns and, as a consequence, for the maintenance treatment in schizophrenia. Data on oral paliperidone and PP1M side effects were not discussed in this review, however they should always be considered in the long-term treatment of schizophrenia. While first generation antipsychotics showed higher rates of extrapyramidal adverse events, an increased risk of metabolic and cardiovascular diseases has been described for second generation antipsychotics. Particularly, there is a greater likelihood of prolactin's elevation in patients treated with oral paliperidone and PP1 compared to placebo and other antipsychotics such as aripiprazole, brexpiprazole and cariprazine.[38] On the other hand, the risk of weight gain and metabolic syndrome with PP1 has been shown to be lower than with other atypical antipsychotics. In a 12-month observational prospective study on real-world patients suffering from schizophrenia and treated with PP1, the proportion of subjects with metabolic syndrome at baseline (33%) did not significantly change neither at 6 months (39.0%) nor at 12 months (29.5%) of PP treatment.[24]

The secondary aim was to analyse clinical healthcare resource utilisation and healthcare costs related to PP-LAI treatment, compared to OA. A lower number of hospitalisations, shorter inpatient length of stay,[30,31,33,35–37] lower total costs, medical costs and all-cause inpatients costs[31,35,37] were found in subjects treated with PP compared to OA. A trend of higher rates of outpatient and pharmacy visits,[31,37] outpatient costs[31,35,37] and pharmacy costs[30,31,33,35–37] in the PP1M

cohort emerged, compared to OA. As already mentioned, a possible explanation for these findings is that LAI treatments are associated with a greater adherence levels, with a resulting higher clinical effectiveness and better tolerability, compared to OA. A stronger clinical effectiveness and lower side effects enhance medications' compliance, producing a cycle where efficacy, tolerability and adherence seem to be both causes and effects of each other. As a consequence, subjects treated with PP are more clinically stable and require less inpatient healthcare resource utilisation/costs, such as lower number of hospitalisations and a shorter period of time, when hospital admission is needed. On the contrary, the LAI specific modality of administration demands monthly PP injections with a healthcare professional, resulting in more frequent outpatient visits/costs and pharmacy costs, but also in higher continuity of care. Finally, the current and previous analysis suggest that the increased outpatient and pharmacy costs associated with PP are offset by the lower total medical costs.

This review should be considered in light of some limitations. First of all, medications' compliance has been evaluated using data from large national databases: coding mistakes are possible and some significant variables that can interfere with adherence patterns are missing (eg severity of the disorders, previous treatments and social support). Moreover, the claim for a filled prescription has been used to assess OA compliance, but it does not imply that the drug was really taken and it could result in a possible adherence overestimation. Finally, there is a lack of data on adherence levels, healthcare resource utilisation and healthcare costs on PP3M and PP6M.

Despite limitations, our findings are noteworthy, as they suggest that paliperidone palmitate should be considered as a good treatment strategy for patients affected by schizophrenia, not only because showed good efficacy and tolerability, but also because PP is associated with a better adherence patterns and more favourable HRU and HC compared to OA.

Funding

No funding was received for this study.

Disclosure

Stefano Bramante has been a speaker for Lundbeck and Janssen. Gabriele Di Salvo has been a speaker for Lundbeck, Angelini and Janssen. Giuseppe Maina is/has been a consultant and/or a speaker and/or has received research grants from Angelini, Boheringer Ingelheim, FB – Health, Janssen, Lundbeck, Otsuka, Innova Pharma. Gianluca Rosso is/has been a speaker and/or consultant from Angelini, Janssen, Lundbeck, Otsuka and Viatris. The authors report no other conflicts of interest in this work.

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