

Paliperidone palmitate in short- and long-term treatment of schizophrenia

Paliperidone palmitato nel trattamento della schizofrenia a breve e a lungo termine

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SUMMARY. Poor adherence to treatment remains a major problem in the management of patients with schizophrenia. In the 60s, first generation antipsychotics in depot formulation have been introduced on the market with the aim to improve adherence to therapy. However, the limited effectiveness on negative symptoms and the tendency to induce extrapyramidal side effects has limited their use. Currently there are five second-generation antipsychotic long-acting formulations and the use of these drugs has definitely changed perspective: they are no more restricted as compounds intended to improve compliance, but they can be considered first-line drugs with proven efficacy and good tolerability. In this narrative review the efficacy and tolerability of paliperidone palmitate, as well as the economic impact of the use of this particular molecule, have been evaluated in the short- and long-term treatment of schizophrenia. Taking into account the results of different studies, paliperidone, especially in his long-acting formulation, can be considered a viable and effective treatment for patients with schizophrenia, both in the short- and in the long term.

KEY WORDS: paliperidone palmitate, schizophrenia, short-term treatment, long-term treatment.

RIASSUNTO. La scarsa aderenza al trattamento rimane un problema consistente nella gestione dei pazienti affetti da schizofrenia. Negli anni '60 gli antipsicotici di prima generazione in formulazione depôt sono stati introdotti sul mercato con l'obiettivo di migliorare l'aderenza alla terapia. Tuttavia, la limitata efficacia sui sintomi positivi e la tendenza a indurre effetti collaterali extrapiramidali ne hanno limitato l'utilizzo. Attualmente esistono cinque antipsicotici di seconda generazione in formulazione long-acting e l'uso di questi farmaci ha sicuramente cambiato prospettiva: non sono più soltanto formulazioni intese a migliorare la compliance, ma possono essere considerati dei farmaci di prima linea, con provata efficacia e buona tollerabilità. In questa rassegna narrativa l'efficacia e la tollerabilità del paliperidone palmitato, oltre all'impatto economico dell'uso di questa particolare molecola, sono state valutate nel trattamento della schizofrenia a breve e a lungo termine. Prendendo in considerazione i risultati di diversi studi, il paliperidone, soprattutto nella sua formulazione long-acting, può essere considerato un valido ed efficace trattamento nei pazienti affetti da schizofrenia sia a breve che a lungo termine.

PAROLE CHIAVE: paliperidone palmitato, schizofrenia, trattamento a breve termine, trattamento a lungo termine.

INTRODUCTION

Poor medication adherence to pharmacological treatment remains one of the most important problems in the management of patients with schizophrenia. Less than 65% of patients presented full adherence to treatment after a few weeks, and this rate dropped to only 25% considering a time of two years¹.

In the 60s, first-generation antipsychotics in depot formulation have been introduced with the aim to improve adherence to pharmacological treatment. However, due to their limited effectiveness on negative symptoms and the high potential to induce extrapyramidal adverse events, long-acting first-generation antipsychotics have obtained a partial success. Currently, there are five second-generation antipsychotics with a long-acting formulation. This opportunity has de-

finately changed the perspective about the utilization of depot antipsychotics: they are not only compounds able to improve the compliance, but they can be considered first-choice drugs with proven efficacy and good tolerability. The first among these drugs to be used was risperidone, which is administered every 2 weeks and requires an oral supplementation for the first 4-6 weeks. Later, it was followed by olanzapine pamoate. It is administered every 2-4 weeks, depending on the dosage, although it can cause in a limited number of cases a "post-injection-syndrome", as a peculiar side effect. Subsequently, paliperidone palmitate 1-monthly (PP1M) was introduced into the market, an atypical antipsychotic that has been approved for the treatment of schizophrenia by the Food and Drug Administration (FDA) on July 31, 2009 and by the European Medicines Agency (EMA) on March 4, 2011, and which is the long-acting formulation of paliperido-

ne, a molecule that is a valid option for short- and long-term treatment of schizophrenia². Compared to long-acting risperidone microspheres and olanzapine pamoate, PP1M has the advantages that it is administered in a single dose every 4 weeks and doesn't need any oral supplementation. Moreover, the drug has minimal hepatic metabolism with no relevant drug interactions, it does not require to be refrigerated and can be administered indifferently in the deltoid or in the gluteal muscle. Aripiprazole long-acting was later introduced, which is administered every 4 weeks and requires an oral supplementation for the first 2 weeks. In more recent time, paliperidone palmitate was introduced in its 3-monthly formulation (PP3M), which is administered in patients previously treated with PP1M for 4 months or more. The dosage is closely connected to that of PP1M previously prescribed to the patient.

PHARMACOKINETIC PROFILE

Paliperidone palmitate is the palmitate ester of paliperidone which is the 9-OH metabolite of risperidone. Paliperidone palmitate belongs to the chemical class of benzisoxazole derivatives. Its chemical name is (9RS)-3[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)viperidi-1-yl]ethyl]2-methyl-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-9-yl hexadecanate. Paliperidone palmitate is hydrolyzed into its active component, paliperidone. The palmitate ester of paliperidone is an aqueous suspension using a nanoparticle technology. Thanks to its extremely low solubility, paliperidone palmitate dissolves slowly after intramuscular injection before being hydrolyzed to paliperidone and absorbed into the systemic circulation. The plasma concentrations gradually rise after a single intramuscular dose to reach maximum at a median T_{max} of 13 days. The drug is released as early as day 1 for as long as 126 days making unnecessary the supplementation with oral paliperidone at beginning of treatment³. Mean T_{max} values of 13-14 days were observed following paliperidone palmitate injection in the deltoid muscle, compared to 13-17 days after injection in the gluteus. The AUC of paliperidone following paliperidone palmitate administration was dose-proportional over a 39 mg-234 mg dose range and less than dose proportional for C_{max} for doses exceeding 78 mg. The median apparent half-life of paliperidone following single-dose paliperidone palmitate administration over the dose range of 39 mg-234 mg ranged from 25 days-49 days. A single injection into the deltoid muscle presented a maximum plasma concentration (C_{max}) 28% higher than the injection in the buttock³. The two injection sites do not presented any differences between the time required to reach the maximum plasma concentration and the area under the curve after 4 injections⁴. The first two injections of 150 mg eq in the deltoid on day 1 and of 100 mg eq on day 8 help to achieve therapeutic concentrations quickly³. The peak-to-trough mean ratio at steady-state after administration of paliperidone palmitate 100 mg eq by injection into the deltoid and the gluteus was 1.8 and 2.2 respectively. Overall, the administration in the deltoid muscle was associated with a higher C_{max} and a T_{max} slightly earlier than the injection into the buttock. The volume of distribution was 391 l and the plasma protein binding after a dose of paliperidone palmitate is about 74%³.

Paliperidone is not extensively metabolized in the liver, as indicated by the presence of 59% of the unchanged medication into urine after a week following administration of a single oral dose of 1 mg immediate-release ¹⁴C-paliperidone. Approximately 80% of the administered radioactivity was recovered in urine and 11% in the feces. In vivo studies have identified 4 metabolic pathways including dealkylation, hydroxylation, dehydrogenation and benzisoxazole scission, but none of these affects more than 10% of the dosage³. The pharmacokinetic profile was similar in poor and extensive metabolizers. Therefore, the distinction between these two extreme classes of metabolizers appears scarcely significant. Although in vitro studies suggested a role for CYP2D6 and CYP3A4 in the metabolism of paliperidone, in vivo results indicated that these isoenzymes play a limited role in the metabolism of the drug. In vitro studies using human liver microsomes also showed that paliperidone does not substantially inhibit the metabolism of drugs metabolized by the various P450 cytochrome isoenzymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4 and CYP3A5. Due to its limited hepatic metabolism paliperidone is not deemed to cause clinically important pharmacokinetic interactions with drugs metabolized by P450 cytochrome³. Furthermore, in a study with oral paliperidone administered to subjects with moderate liver failure (class B according to Child-Pugh classification), plasma concentrations of free paliperidone were similar to those of healthy subjects. Unfortunately, there have been no studies with paliperidone in patients with severe liver failure³. Paliperidone palmitate has not been systematically studied in patients with kidney failure. However, based on a limited number of observations and pharmacokinetic simulations, the dose of paliperidone palmitate should be reduced in subjects with mild kidney failure, but its administration is not recommended in patients with moderate or severe kidney failure. Although paliperidone palmitate was not studied in patients with moderate or severe kidney failure, the administration of a single dose of 3 mg of paliperidone ER was studied at renal level in subjects with varying degrees of kidney failure. Elimination of paliperidone is directly correlated with creatinine clearance: total clearance of paliperidone was reduced in subjects with impaired renal function by 32% on average in mild ($CrCl=50$ mL/min to <80 mL/min), 64% in moderate ($CrCl=30$ mL/min to <50 mL/min), and 71% in severe ($CrCl=10$ mL/min to <30 mL/min) kidney failure, corresponding to an average increase in exposure (AUC_{inf}) of 1.5 fold, 2.6 fold, and 4.8 fold, respectively compared to healthy subjects. Based on pharmacokinetic simulations and a limited number of observations, subjects with a mild kidney failure should be exposed to an initial dose of paliperidone palmitate of 156 mg on day 1 and 117 on day 8. Finally, no dose adjustments are needed based on age, race, sex and tobacco-smoking habits³.

PHARMACODYNAMIC PROFILE

Paliperidone palmitate is hydrolyzed to paliperidone, the major active metabolite of risperidone. The exact mechanism of action of paliperidone is not known but it seems to be mediated through a combination of central dopamine D₂ and serotonin 5HT_{2A} receptor antagonism. An antagonism for α_1 and α_2 adrenergic receptors and H₁ histaminergic receptors

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is also presented, while there is no affinity for cholinergic muscarinic or α_1 - and α_2 -adrenergic receptors. In vitro, the pharmacological activity of the (+)- and (-)- paliperidone enantiomers is qualitatively and quantitatively similar³.

OBJECTIVE

The aim of the present narrative review is to gather a selection of evidences from the literature concerning the efficacy and the tolerability of paliperidone palmitate both in the short- and in the long-term treatment of schizophrenia, including a comparison with other similar molecules. A secondary aim of the present paper was to evaluate the pharmacoeconomic aspects of the use of paliperidone palmitate.

MATERIALS AND METHODS

An electronic search was performed on the MEDLINE database through the PubMed search engine. Studies reported in the present paper were selected for their similar inclusion and exclusion criteria. Patients were to be adults with a diagnosis of schizophrenia according to the criteria reported in the Diagnostic and Statistical Manual of Mental Disorders, either in its fourth edition (DSM-IV)⁵ or in its fourth edition with text revision (DSM-IV-TR)⁶. Patients were excluded if they manifested substance abuse or substance dependence disorders, or if they showed hypersensitivity or intolerance to either paliperidone or risperidone. Another exclusion criteria common to all studies included was the presence of medical conditions that could constitute a direct contraindication to the administration of paliperidone, including pregnancy and nursing. To provide a more detailed overview, different types of studies were included, such as randomized controlled trials, post-hoc analyses and retrospective longitudinal cohort studies. To properly represent real-world expenditures, studies concerning pharmacoeconomic aspects were included if they evaluated the costs related to the use of paliperidone palmitate, regardless of the presence of comorbidity with substance use disorders. More details on the included studies are shown in Table 1.

SHORT-TERM STUDIES PALIPERIDONE PALMITATE ONE MONTHLY

The short-term efficacy and safety of PP1M were assessed in many studies (Table 2).

The first study⁷ was a double-blind study drug. The study was divided in three phases over about 11 weeks: a screening phase of 5 days, a second phase of 7-day with hospitalization and assignment to one of four open-label once-daily morning doses of oral paliperidone, and a third one of 64 days, with double-blind treatment, where patients were randomized 1:1:1 to receive either PP1M 50 mg eq, PP1M 100 mg eq or placebo. Patients received a total of three separate injections on days 1, 8, and 36. A total of 266 patients were enrolled: of these, 247 (92.9%) entered the oral run-in-phase and continued into the double-blind phase. Among the 247 randomized patients, 51% (125 patients) completed the double-blind phase lasting 64 days. The number of patients allocated in the PP1M group who completed the trial was doubled respect to what observed for the placebo group. Regarding the primary efficacy measure, both doses of PP1M led to a significant dif-

ference ($p \leq 0.001$) in the mean change in Positive and Negative Syndrome Scale (PANSS)⁸ total score from baseline to endpoint compared with placebo. Each group presented significant differences from day 8 in the PP1M and were maintained until the end of the double-blind phase ($p \leq 0.011$). Furthermore, both the dosages of PP1M (50 mg eq and 100 mg eq) differed from placebo ($p \leq 0.002$) and, generally, the treatment with PP1M also presented a significant improvement in the five PANSS factor scores and in response rates at 30%. Even the percentage improvement in PANSS total score showed a significant difference in both doses of PP1M compared with placebo ($p \leq 0.001$). In addition, the Clinical Global Impression-Severity (CGI-S)⁹ presented an improvement in symptoms at endpoint with 50% of placebo patients being classified as marked, severe or extremely severe, compared with 37% of patients treated with 50 mg eq of PP1M and 32% of those treated with 100 mg eq. Both doses of PP1M resulted superior to placebo ($p \leq 0.004$) in reducing CGI-S scores.

The second short-term study¹⁰ is a 13-week, randomized, double-blind, dose-response study. It included a 7-day screening phase, followed by a 13-week, double-blind treatment period. Patients were randomly assigned (1:1:1:1) to fixed doses of PP1M (50, 100, 150 mg eq.) or placebo. All patients received four intramuscular injections of PP1M or placebo on days 1, 8, 36 and 64. From the first to the second injection, patients were hospitalized. Of the 473 patients screened, 388 (82%) were randomly assigned to one of the treatment groups and 187 (39.5%) completed the 13-week study. The mean (SD) duration of exposure in the PP1M 50, 100, and 150 mg eq groups ranged between 52.8 and 64.8 days. In the PP1M group, about the 47-55% of the patients received all four injections of double-blind phase, while in the placebo group only the 41% of them. About the primary efficacy, researchers found in the palmitate 1 monthly 100 mg eq a significant improvement in the PANSS total score compared to the placebo group ($p=0.019$), while the secondary efficacy measurement showed an improvement on the Social Performance Scale (PSP)¹¹ score in both group (respectively $p < 0.001$ and $p=0.004$ in the PP1M 100 mg eq and 50 mg eq groups). The improvement in CGI-S was significant only for PP1M 100 mg eq ($p=0.01$). The PP1M 100 mg eq group also showed a significant improvement in all five PANSS factor scores ($p < 0.04$) and in the three PANSS subscale scores ($p \leq 0.03$), while the percentage of responders resulted to be greater ($p < 0.02$). At this dose, a significant onset of effect was evident on day 36 and was presented at all subsequent time point to the endpoint.

In a short-term, randomized, placebo-controlled study¹² researchers assessed the efficacy and safety of 3 doses of paliperidone in adults with acutely exacerbated schizophrenia. The study included a 7-day screening period and a 13-week double-blind treatment period. Eligible patients were randomly assigned (1:1:1:1) to fixed doses of PP1M (25, 100, or 150 mg eq) or placebo. Patients received their assigned treatment on days 1, 8, 36 and 64. From day 1 to day 8 patients were hospitalized. From a total of 855 screened patients, 652 (76%) were randomly assigned to one of the four treatment groups and 333 of them (51%) completed the study (262 in the total PP1M group and 71 in the placebo group). All the four injections of the double-blind study were more administered in patients from the PP1M group (56%

Table 1. Main characteristics of the studies.

Authors	Type of study	N	Clinical baseline characteristic	Duration
Kramer et al. ⁷	RM, DB, PB-controlled study	266 patients, 197 in the ITT analysis	PANSS TS between 60-120	9 weeks
Gopal et al. ¹⁰	RM, DB, dose-response study	388 patients	PANSS TS between 70-120	13 weeks
Pandina et al. ¹²	MC, RM, DB, PB-controlled, phase 3 study	652 patients	PANSS TS between 60-120	13 weeks
Nasrallah et al. ¹³	MC, RM, DB, PB-controlled, parallel-group, dose-response study	514 patients	PANSS TS between 70-120	13 weeks
Hargarter et al. ¹⁵	Non-RM, single-arm, MC, OL, prospective, interventional study	212 patients	PANSS TS above 80	6 months
Kwon et al. ²⁰	MC, RM, OL, comparative study	154 patients	Patients not satisfied about their current oral atypical antipsychotic therapy	21 weeks
Si et al. ²³	MC, OL, single-arm, prospective study	616 patients in the safety analysis set and 610 of them in the full analysis set	PANSS TS above 70	13 weeks
Schreiner et al. ²⁵	Post-hoc analysis of a prospective, interventional, single-arm, international, MC study	46 patients	Clinically stable but symptomatic	6 months
Hough et al. ²⁶	DB, RM, PB-controlled study	849 patients in the transition phase, 681 in the maintenance phase and 410 in the DB phase	PANSS TS below 120	33 weeks
Gopal et al. ²⁷	OL extension of a DB study	388 patients	PANSS TS below 120	52 weeks
Ravenstijn et al. ²⁸	MC, RM, OL, parallel-group, phase-I study	328 patients, of which 74 in panel A, 129 in panel B, 25 in panel C and 100 in panel D	PANSS TS below 70	53-79 weeks
Savitz et al. ²⁹	MC, DB, parallel-group, phase-3 study	1016 patients	Clinically stable (PANSS TS below 70)	48 weeks
Fleischhacker et al. ³¹	MC, RM, DB, active-controlled, parallel-group, comparative study	749 patients	PANSS TS between 60-120	53 weeks
Pandina et al. ³²	MC, RM, DB, double-dummy, active-controlled, parallel-group, non-inferiority comparative study	1220 patients	PANSS TS between 60-120	13 weeks
Li et al. ³³	OL, rater-blinded, parallel-group study	452 patients	PANSS TS between 60-120	13 weeks
McEvoy et al. ³⁶	MC, DB, RM clinical trial	311 patients	-	24 months
Naber et al. ³⁹	Phase 3b, MC, OL, rater-blinded, RM, non-inferiority study	295 patients	CGI-S between 3 and 5 (included)	28 weeks
Pesa et al. ⁴⁴	Retrospective, observational study	5183 patients	-	12 months
Lefebvre et al. ⁴⁵	Retrospective longitudinal cohort study	6872 patients	-	12 months
Pilon et al. ⁴⁷	Retrospective longitudinal cohort study	24300 patients	-	12 months

DB: double-blind; ITT: intent-to-treat; MC: multicenter; OL: open-label; PB: placebo; RM: randomized; TS: total score.

received 25 mg eq, 61% received 100 mg eq and 59% received 150 mg eq) than in those from the placebo group (48%), while the duration of exposure was similar in both group (from 65 to 67 days for the 3 PP1M groups and 58 days for the placebo group). Compared to placebo, researchers

found a significant and dose-related change in PANSS total score for each of the three PP1M groups and on day 92 the changes were different between placebo and PP1M 25 mg eq ($p=0.02$), 100 mg eq and 150 mg eq (both $p<0.001$). Considering the PSP scores, an improvement was found in the

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Table 2. Short term studies paliperidone palmitate 1 monthly: assessments and main findings.

Authors	Assessment	Main effect of treatment with PP1M
Kramer et al. ⁷	Patients who finished the OL run-in phase were randomized to paliperidone palmitate (n:79, 50 mg eq im; n:84, 100 mg eq im) or PB (n:84)	Compared to PB: reduction in PANSS TS, all the five PANSS factor scores, CGI-S score
Gopal et al. ¹⁰	Patients were assigned to paliperidone palmitate group (n:94; 50 mg eq; n:97, 100 mg eq; n:30, 150 mg eq), paliperidone palmitate 150 mg eq/PB (n:31) or PB (n:138)	Compared to PB: improvement in PANSS TS, PANSS factor scores, PANSS subscale scores and CGI-S in PP1M; while PSP score appeared increased both in PP1M 50 mg eq and 100 mg eq groups
Pandina et al. ¹²	Patients were assigned to paliperidone palmitate (n:160; 25 mg eq; n:165, 100 mg eq; n:163, 150 mg eq) or PB (n:164)	Compared to PB: each paliperidone palmitate group showed a reduction in PANSS TS, while the PSP score, the CGI-S score, the PANSS Marder factor and PANSS subscales scores appeared to be improved in 100 mg eq and 150 mg eq paliperidone palmitate group
Nasrallah et al. ¹⁴	Patients were assigned to paliperidone palmitate (n:130, 25 mg eq; n:128, 50 mg eq; n:131, 100 mg eq) or PB (n:125)	Compared to PB: all paliperidone palmitate groups showed improvement in PANSS TS
Hargarter et al. ¹⁵	From the original sample, 212 patients were evaluated for safety and 207 for efficacy	PANSS TS, positive, negative and general psychopathology showed a decrease, as well as the Marder factor scores and the CGI-S score. The mini-ICF-APP and the PSP (single domain and total score) improved, as well as the SWN-S total score and the TSQM global satisfaction score. Quality of sleep and daytime drowsiness gained
Kwon et al. ²⁰	Patients were assigned to immediate switch group (n:78) or delayed switch group (n:76)	After switching to PP1M, both group showed an improvement in PANSS TS, PSP, MSQ score and in TSQM (effectiveness, convenience and global satisfaction)
Si et al. ²³	All patients were switched to PP1M	Compared to the baseline: improvement in PANSS TS, PANSS Marder factor scores (positive symptoms), CGI-S and PSP. Significant changes were also reported in MARS and MPQ after using PP1M
Schreiner et al. ²⁵	Patients were followed after switching from aripiprazole to PP1M	Treatment with PP1M appeared correlated to improvement in PANSS TS, PANSS Marder factors scores, PSP total score and Mini-ICF-APP score

OL: open-label; PB: placebo; PP1M: paliperidone palmitate 1 monthly; TS: total score

PP1M 100 mg eq ($p=0.007$) and 150 mg eq ($p<0.001$) groups, as well as in CGI-S scores ($p\leq 0.005$), in all the 5 PANSS Marder factor scores¹³ ($p\leq 0.01$) and in the 3 PANSS subscale scores ($p\leq 0.02$). Generally, a significant change in PANSS total score was observed already at day 8 in the 25 and 150 mg eq treatment groups (as consequence of the initial 150 mg eq dose on day 1) and from day 22 until the end point in all the three PP1M groups. Response to treatment appeared to be more significantly in patients in the PP1M (25 mg eq. group: 33.5%, $p=0.007$; 100 mg eq. group: 41.0%, $p<0.001$; 150 mg eq. group: 40.0%, $p<0.001$) compared to placebo (20.0%), as well as the quality of sleep on a visual analogue scale significantly improved from baseline to end point in the PP1M 100 and 150 mg eq. groups compared to placebo ($p\leq 0.03$).

In a 13-week, multicenter, randomized, double-blind, parallel-group study¹⁴, researchers evaluated the efficacy, safety, and tolerability of fixed 25, 50 and 100 mg eq doses of PP1M compared to placebo. All patients were hospitalized from day 1 through day 8 of treatment. The study included a 7-day screening period and a 13-week double-blind treatment period. Patients were randomly assigned in a 1:1:1:1 ratio to placebo injections (intralipid) or intramuscular fixed doses of PP1M (25, 50, or 100 mg eq). As efficacy variable, researchers evaluated primary the change from baseline to end-point in PANSS total score and, secondary, changes in

CGI-S and Personal and PSP scale. Other efficacy variables included PANSS subscales, PANSS Marder factor scores and treatment responder rate. Of the 518 randomized patients, 263 (51%) patients ended the 13-week double-blind phase. Researchers found in all PP1M groups a significantly improved change in PANSS total scores compared to placebo (25 mg eq, $p=0.015$; 50 mg eq, $p=0.017$; 100 mg eq, $p<0.001$). Conversely, about the secondary measures of effectiveness there were not significant changes between paliperidone groups and placebo. Considering as response criterion a decrease at least of 30% from baseline to end point in PANSS total score, there were more treatment responders in the PP1M 25 mg eq (45.7%; $p=0.015$) and 100 mg eq (51.9%; $p<0.001$) than in the placebo group (31.2%).

In a non-randomized, single-arm, multicentre, open-label, 6-month, prospective interventional study¹⁵, researchers evaluated the efficacy of PP1M in patients with acute schizophrenia previously unsuccessfully treated with oral antipsychotics. The 6-month study period started with the first PP1M injection and, within 4 weeks, the interruption of their previous oral antipsychotic. PP1M was administered at 150 mg eq on day 1 and 100 mg eq on day 8. Subsequently, it was administered once-monthly using flexible dosages (between 50 and 150 mg eq) on days 38, 68, 98, 128 and 158. A total of 212 patients were switched to PP1M, receiving at least one

dose, most due to lack of efficacy or compliance (respectively 45.8% and 34.9%). After switching to paliperidone palmitate, 66.7% patients met the criteria for clinical response and 43.5% patients achieved an improvement greater than 50% in mean PANSS total score. Mean PANSS total score resulted to be significantly decreased already at day 8 ($p<0.0001$). Also the PANSS Positive, Negative and General Psychopathology subscale and Marder factor scores showed a significant reduction, as well as the CGI-S score demonstrated a significant decrease in disease severity ($p<0.0001$) and the proportion of patients rated markedly ill or worse decreased from baseline to endpoints (respectively from 75.1% to 20.5%). About the CGI-C, most of the patients who switched to PP1M showed an improvement from baseline. The Mini-ICF-APP¹⁶ total scores and the PSP total score increased significantly (demonstrated also by an improvement in all PSP domain scores, $p<0.0001$). In particular, the Mini-ICF-APP total scores demonstrated a significant improvement in the illness-related disorders of activity and participation. Quality of sleep and daytime drowsiness showed significant gain. Other significant improvements were observed also in the Subjective Well-Being Scale (SWN-S)¹⁷ total score and in the Treatment Satisfaction Questionnaire for Medication (TSQM)¹⁸ global satisfaction score, where the last one showed a better scores related to medication effectiveness ($p<0.0001$) and convenience ($p<0.0001$). The side effects domain score did not reach significant improvements, but only a trend ($p=0.0555$). Also the Physician's satisfaction scores demonstrated a significant improvement for all aspects of treatment ($p<0.0001$). About safety and tolerability, 63.7% of patients experienced at least one treatment-emergent adverse event (TEAE). Fortunately, the 89.1% of TEAEs were rated as mild or moderate in intensity and generally did not cause a changing in PP1M dose (69.7%). The most common TEAEs were injection-site pain (13.7%), insomnia (10.8%), psychotic disorder (10.4%), anxiety and headache (6.1% each). In 19 patients (9.0%), AEs led to early termination of the study, such as psychotic disorder in 4 patients (1.9%), schizophrenia and amenorrhea in 2 patients each (0.9% each). Among the total patient population, 12 had a potentially prolactin-related TEAE (5.7%), with amenorrhea (2.4%), erectile dysfunction (1.4%), hyperprolactinemia (0.9%), gynecomastia (0.5%) and galactorrhea (0.5%). Administration of PP1M was generally associated with a significant reduction in extrapyramidal symptom (with mean Extrapyramidal Symptom Rating Scale (ESRS)¹⁹ total scores from 3.8 to 2.3, $p<0.0001$). During the study 40 patients (22.5%) had an increase in body weight greater than 7%. Two cases of fatal outcome were reported (due to acute myocardial stroke the first and to completed suicide the second), but both were not considered related to the treatment.

In a multicenter randomized open-label comparative study²⁰ researchers evaluated the patients' satisfaction about treatment with PP1M. Patients reported dissatisfaction about their medication, measured by score 4 or less on the Medication Satisfaction Questionnaire (MSQ)^{21,22}, and hoped about a potential benefit by switching treatment. MSQ, TSQM, PANSS and PSP scale were assessed by researchers at each visit from the baseline. Patients were randomized to the delayed switch group or to the immediate switch group. Of 170 participants who were screened, 154

were randomized and 134 accessed to the full analysis set. Of them, 126 were included in the per-protocol set. Finally, 85 patients were included in the strict per-protocol set. After switching to PP1M, the MSQ score increased with a significant change both in the per-protocol set and in the strict per-protocol set (both $p<0.0001$). The increase was observed in the immediate switch group (0.78 ± 1.32) and in the delayed switch group (0.37 ± 1.01), respectively ($p=0.05$). The mean MSQ score increased in the adjustment period of oral medication ($p=0.036$) and after the switch ($p=0.01$) in the delayed switch group. In the TSQM, patients on PP1M showed an improvement in the mean change from baseline to endpoint about effectiveness, convenience and global satisfaction (in the immediate switch group respectively $p=0.0003$, $p<0.0001$ and $p=0.026$; in the delayed switch group respectively $p<0.0001$, $p<0.0001$ and $p<0.0001$), while there was no significant change in the TSQM side effects. In the PANSS total score researchers observed a significant decrease at the endpoint: 5.37 ± 17.32 points in the immediate switch group ($p=0.0135$) and 4.76 ± 13.5 in the delayed switch group ($p=0.0053$). The two groups showed similar changes in the TSQM and PANSS scores. At the endpoint, the PSP total score increased in the immediate switch group by 3.49 ± 12.71 points ($p=0.0279$) and in the delayed switch group by 3.36 ± 10.85 ($p=0.0137$). In the safety analysis set, from 141 patients, 76 patients from the immediate switch group (72.4%) and 65 patients from the delayed switch group (56.9%) showed at least one adverse event (65.2% of the total amount). Akathisia, insomnia and injection site pain were common (respectively 14 patients each the first and the second, 9.9%, and 9 patients the third, 6.4%). In the immediate group 9 patients experienced akathisia (11.8%), 8 patients presented insomnia and injection site pain (10.5%, each), 7 patients experienced anxiety (9.2%), 5 patients showed sedation (6.6%) and 4 patients presented headache and fatigue (5.3%, each), while in the delayed group 6 patients experienced insomnia and injection site pain (9.2%), 5 patients presented schizophrenia symptom aggravation, headache, and akathisia (7.7%). Serious adverse events appeared in 3 patients from the immediate switch group (3.9%) and in 2 patients from the delayed switch group (3.1%).

In a flexible-dose, open-label, single-arm, multicenter, prospective study²³, researchers analyzed the efficacy and the safety of PP1M. All patients referred the preference to switch to another antipsychotic consequently to dissatisfactory therapeutic effect. The study was divided into three phases: a 1-week screening phase, a 13-weeks acute treatment phase and a 12-months follow-up phase. During the acute treatment phase, patients received 150 mg eq dose of PP1M on day 1 and 100 mg eq PP1M dose on day 8 followed by a monthly maintenance dose between 75 and 150 mg eq on days 36, 64, and 92. Of the 610 enrolled patients 443 (72.6%), treated with PP1M, showed more than 30% decrease in PANSS total score (from baseline to end of 13 weeks). Similarly, from the 444 patients in the per protocol analysis set, 391 patients (90.7%) showed more than 20% decrease in PANSS total score, 364 patients (84.5%) more than 30% and 274 patients (63.6%) more than 50%. All the PANSS Marder factor scores significantly changed from baseline to end of 13 weeks ($p<0.001$), mostly in positive symptoms. Both CGI-S and PSP scores changed from baseline to end of 13 weeks (both $p<0.001$). The involvement

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evaluation questionnaire subscale and total scores, the medication preference questionnaire (MPQ) scores and medication adherence rating scale score (MARS)²⁴ scores changed from baseline to end of 13 weeks ($p<0.001$). At the baseline 60% patients preferred injections over tablets, while after 13 weeks the number of patients who preferred injections increased to 78%. This preference could be explained by the simplicity of the injections (50%), the absence of remembering to take medication everyday (48.4%), the lowering of adverse effect and a greater effectiveness on the symptoms, such as auditory hallucination (32%). In the analysis set, from a total of 616 patients, 198 showed at least one TEAE (32.1%). The most common TEAEs observed were EPS (8.4%), insomnia (4.7%), constipation (4.4%), upper respiratory tract infection (4.1%) and akathisia (2.3%). Worsening of psychotic symptoms was observed in 8 patients, EPS in 3 patients, insomnia, auditory hallucination, bradycardia, depression, sinus bradycardia, akathisia, increased hepatic enzymes levels, lung infection, hematuria and acne each in 1 patient and they induced a permanent discontinuation of treatment. The most common EPS-related TEAEs were parkinsonism in 55 patients (8.9%), hyperkinesia in 18 patients (2.9%), dystonia and tremor both in 2 patients (0.3%), and dyskinesia in 1 patient (0.2%). Nine patients showed prolactin-related TEAEs in the acute treatment phase, with increase of prolactin levels in 5 patients (0.75%), delayed menses in 2 patients (0.3%) and oligomenorrhea/irregular menstruation or menstrual disorder in 1 patient (0.2%). In 1 patient, TEAEs were related to suicidality. About abnormalities in ECG, 170 patients (27.6%) presented them at baseline and 83 patients (13.5%) at the end of 13 weeks. Seven patients treated with PP1M presented increasing of body weight, from 64.42 ± 12.44 kg at the baseline to 65.5 ± 12.20 kg at the end of 13 weeks. Changes greater than 7% from baseline in weight were presented in 64 patients (10.4%), while 48 patients (7.8%) had significant weight gain and 16 patients (2.6%) had significant weight loss at the end of 13 weeks.

In a prospective, interventional, single-arm, multicenter 6-month study²⁵, the researchers evaluated the efficacy and the safety of PP1M in 46 patients previously treated unsuccessfully with aripiprazole. The study was divided into a 7-day screening period and a 6-month prospective study period. On day 1, PP1M 150 mg eq was administrated and, on day 8, 100 mg eq. Subsequently, the maintenance dose (between 50-150 mg eq) was given once-monthly. A significant and clinically relevant improvement was found with PP1M treatment in mean PANSS total scores from baseline to endpoint

($p<0.0001$). This change resulted to be greater than 20% and than 50% respectively in 52.2% and 21.7% of patients. A significant improvement was observed also in PANSS Marder factor scores (negative subscale $p<0.0001$ at month 2 and $p=0.0006$ at the endpoint; disorganized thoughts $p<0.0001$ at day 8 and $p<0.0001$ at the endpoint; anxiety/depression $p=0.0063$ at day 8 and $p=0.0031$ at the endpoint). About the PSP total score, a functional improvement was observed at the endpoint in personal and social performance ($p=0.0409$), confirmed in the socially useful activities, as well as in the Mini-ICF-APP score ($p=0.0079$). TEAEs were observed in 32 patients (69.6%) and most of them were rated as mild or moderate (93.3%). The most common TEAE was akathisia (8.7%), followed by weight increase and abnormal weight gain (6.5%) and injection site pain (5% or more). EPS significantly improved at the endpoint, with a mean change in the ESRS total score ($p=0.0456$). Considering blood prolactin plasma levels, two patients (4.3%) presented hyperprolactinemia.

LONG-TERM STUDIES PALIPERIDONE PALMITATE ONE MONTHLY

A number of studies also evaluated efficacy and safety of PP1M in the long-term treatment of schizophrenia (Table 3).

The first double-blind, randomized, placebo-controlled study²⁶ was divided in 5 phases: the first phase was a 7-day screening and oral tolerability testing phase; the second phase was a 9-week open-label transition phase where eligible patients were switched and received once-monthly injections of flexibly-dosed PP1M (50 mg eq on days 1 and 25, 50, or 100 mg eq on day 8); the third phase was a 24-week open-label maintenance phase during which stable patients (PANSS score less than 75 at week 9) received flexibly-dosed of PP1M (25, 50, or 100 mg eq) for the first 12 weeks, followed by 12-week treatment at the established maintenance dose; the fourth phase was a variable-duration, event-driven double-blind phase, where stabilized patients were randomized in a 1:1 ratio to receive either PP1M or placebo; the fifth and final phase was an optional 52-week open-label extension phase. The double-blind phase finished in case of relapse or withdrawal or until the study was completed. A significant delay in time-to-relapse was noted in the continuous PP1M compared to the placebo group ($p<0.0001$), with fewer relapse event rates (respectively 10% and 34% of patients in the different groups). The PP1M group also showed a relatively stable mean PANSS total scores in the double-blind

Table 3. Long term studies paliperidone palmitate 1 monthly: assessments and main findings.

Authors	Assessment	Main effect of treatment with PP1M
Hough et al. ²⁶	During the DB phase, patients were randomized to PP1M (n:206) or to PB (n:204)	Compared to PB: treatment with PP1M showed a significant delaying time to relapse and less relapse event; PANSS TS, CGI-S and PSP scores appeared stable
Gopal et al. ²⁷	Patients, who were randomly assigned to PB (n:153) or to PP1M (n:161) in the DB phase or who were in the transition/maintenance phase (n:74), were treated with PP1M in the OLE phase	Treatment with PP1M showed improvement in PANSS TS, CGI-S

DB: double-blind; OLE: open-label extension; PP1M: paliperidone palmitate 1 monthly; PB: placebo; TS: total score.

phase, while it significantly worsened in the placebo group ($p<0.0001$). A similar trend was showed also in CGI-S and PSP scores.

The second²⁷ long-term study lasted 52-week and was structured as open-label. To access to the open-label extension, patients had to complete the double-blind study²⁶ without relapses and had to receive at least one injection of PP1M. Based on the study phase, patients were divided in 3 groups: the first one included patients on placebo in the double-blind phase and switched to PP1M in the open-label extension (PBO/PP1M), the second one included patients on PP1M both in the double-blind and in the open-label phases (PP1M/PP1M), the third one included patients in the transition or maintenance phases who directly entered the open-label extension and received PP1M (TM/PP1M). During the open-label extension, all patients received PP1M, first at an initial dose of 50 mg eq and then at flexible-dosing (25, 50, 75, or 100 mg eq), once every 4 weeks for 12 dosing intervals. A total of 388 patient were enrolled in the open-label extension and 288 (74%) completed the study. Of the 388 patients who entered the open-label extension, 314 (82%) of them received PP1M for at least 252 days, while the median treatment duration was 338 days. Before entering the open-label extension, all patients showed a clinically significant improvements in schizophrenic symptoms, as seen by improvements in PANSS total scores during the transition and maintenance phases. In the double-blind phase, the PP1M group showed relatively stable mean scores, while it worsened in the placebo group. During the open-label extension an improvement was observed in all the three groups treated with PP1M. The researchers observed the greatest improvement in mean PANSS total scores [mean (SD): -8.4 (19.43)] in the PBO/PP group. Also, the PANSS subscale scores showed similar results. During the transition and maintenance endpoint and the maintained in the double-blind phase, the CGI-S scores showed an improvement in the PP1M group: at open-label extension baseline the median CGI-S scores were 3.0 (range: 1-6) for all groups and the median scores remained stable at open-label extension endpoint in the PBO/PP1M group (3.0, range: 1-7) and in the PP1M/PP1M group (3.0, range: 1-5), while it showed improvement in the TM/PP1M group (2.0, range: 1-5). The PSP scores improved during the transition and maintenance phases but worsened during the double-blind phase of the previous study in the placebo group. All three groups showed improvement in personal and social functioning during the open-label extension, especially in the PBO/PP1M group. The mean PSP score improved from the open-label extension baseline (69.3) to the

endpoint (73). The mean (SD) change in PSP scores also improved from transition from baseline to open-label extension endpoint: 7.0 (15.21) in PBO/PP1M group, 7.6 (11.86) in the PP1M/PP1M group and 8.6 (11.03) in the TM/PP1M group.

SHORT-TERM STUDIES PALIPERIDONE PALMITATE THREE MONTHLY

Recent studies evaluated efficacy, safety and tolerability of PP3M (Table 4).

A multicenter, randomized, open-label, parallel-group, phase-1 study²⁸ was divided into 4 panels (A, B, C and D): each panel included a 21-day screening phase and an open-label treatment phase comprising 2 sequential single-dose treatment periods, called period 1 and period 2. Panels B and D also included an extension period. Enrolled patients were randomized to one of the treatment groups (except panel C). In the open-label phase (period 1), patients received paliperidone immediate-release (IR) solution 1 mg, while, during period 2, a single-dose injection of PP3M. Patients were followed in panels A and C for about 53-58 weeks, while in panels B and D they were followed for more than 26 weeks. The doses administered during period 2 were different in each panel (in panel A 300 mg eq; in panel B 75, 150, 300 or 450 mg eq; in panel C 150 mg eq; in panel D 175, 350 or 525 mg eq). In panel A researchers evaluated the local tolerability and safety of PP3M formulation and confirmed the release profile, while in panels B and D safety and tolerability of a single-dose of PP3M were assessed. Patients were enrolled in panel B and C only after the ending of panel A and, similarly, enrollment in panel D was initiated only after the ending of panel B. From a total of 328 enrolled patients (panel A, 74; panel B, 129; panel C, 25; and panel D, 100), 325 received 1 mg intramuscular paliperidone during period 1, 308 received PP3M (from 75mg eq to 525mg eq) and 245 completed the study. Of 325 patients, 87 subjects (26.8%) during period 1 and 227 subjects (73.7%) during period 2 experienced at least 1 TEAE. Most of them was rated as mild to moderate in severity. The most common TEAEs in all the panels during period 1 was headache in 14 patients, while during period 2 were nasopharyngitis and headache in 34 patients each, injection-site-related TEAE in 25 patients, weight increase, backpain in 16 patients each and anxiety in 14 patients. On the contrary, 35 patients reported more than 1 serious TEAEs. The most common serious TEAEs were psychiatrically related: in Panel A 3 patients referred suicidal ideation or presented agitation, depression and psychotic

Table 4. Short term studies paliperidone palmitate 3 monthly: assessments and main findings.

Authors	Assessment	Main effect of treatment with PP3M
Ravenstijn et al. ²⁸	From the starting sample, 325 patients received 1 mg intramuscular of PP1M and 308 of them received PP3M	Both group presented similar safety and tolerability
Savitz et al. ²⁹	Patients were randomized to PP3M (n:504) or PP1M (n:512)	Both groups presented similar changes in PANSS TS and subscales scores, Marder factor scores, CGI-S and PSP scores; PP3M appeared as efficacy as PP1M

PP1M: paliperidone palmitate 1 monthly; PP3M: paliperidone palmitate 3 monthly; TS: total score

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disorder; in panel B and D psychotic disorder and schizophrenia were observed (respectively 4 patients each and 2 patients each). Furthermore 7 patients stopped the study because of TEAEs: 3 subjects in panel A presented anxiety, suicidal ideation, hypertension, 3 subjects in panel B presented myocardial ischemia, psychotic disorder, metastatic malignant melanoma, muscle spasticity and dysphemia and 1 subject in panel D showed psychotic disorder. The EPS scales did not present significant changes across all the panels. No clinically relevant changes were observed in vital or hematology, chemistry, urinalysis parameters in any of the 4 panels, as well as the electrocardiograms (except for 1 patient from panel B which reported QTcF>500 milliseconds at day 140 and 1 patient from panel D which reported QTcF>480 milliseconds at day 224; anyway they were considered not clinically relevant). Only 1 death happened during the study (in panel B), but it was the result of a metastatic melanoma and not related to the study medication.

A double-blind, parallel-group, multicenter, phase-3 study²⁹ evaluated the non-inferiority of PP3M to PP1M. The study was subdivided in 4 phases: the first one was a 3-week screening, the second one a 17-week open label stabilization at flexible doses, the third one a 48-week double-blind at fixed doses and the fourth and last one a follow-up phase. In the open label phase, all patients were treated with PP1M for 17 weeks: at day 1 they received 150 mg eq, then at day 8, 100 mg eq. Subsequently, at weeks 5 and 9, they were treated with a flexible dose (from 50 to 150 mg eq). The dose was repeated at week 9. To enter the third phase, patients had to be evaluated as clinically stable. During the double-blind phase, patients were randomized 1:1 and received at week 17, 29, 41 and 53 a fixed dose of PP1M (50, 75, 100 or 150 mg eq) or a fixed dose of PP3M (175, 263, 350 or 525 mg eq). The patients in the PP3M group received active medication every 3 months and, with the purpose of ensuring the blinding, received matched placebo injections (20% intralipid) in the months free from active medication. To judge the efficacy of the treatment with PP3M, researchers evaluated the percentage of patients who remained relapse-free³⁰. Of 1429 patients enrolled in the open label phase, 1016 (71%) were randomized to the double-blind phase (504 in the PP3M group and 512 in the PP1M, respectively). Discontinuation during the open label phase was due to withdrawal of consent in 118 patients (8%) and to lack of efficacy in 117 patients (8%). Of the 1016 randomized patients, 948 were included in the per protocol analysis set (458 in the PP3M group and 490 in the PP1M group, respectively), while 995 patients were included in the double-blind analysis set (483 in the PP3M group and 512 in the PP1M group, respectively). At the end of the study, 842 (83%) randomized patients, including the patients with relapse, were evaluated (84% in the PP3M group and 82% in the PP1M group, respectively). In both groups, patients showed a relapse event during the double-blind phase (8% in the PP3M group and 9% in the PP1M group, respectively). Relapse was indicated by an increase greater than 25% of the PANSS total score or by psychiatric hospitalization (5% and 3% in the PP3M group and 5% and 4% in the PP1M group, respectively). Similar changes were observed in both groups from the baseline to the endpoint of phase 3 in PANSS total and subscale scores, Marder factor scores, CGI-S and PSP scores, as well as both groups showed a symptomatic remission for the last 6 months after phase 3 (58% in the PP3M

group and 59% in the PP1M group, respectively). In the end, PP3M appeared as effective as PP1M. TEAEs were experienced by 59% of patients and they were equally presented in both groups (68% in the PP3M group and 66% in the PP1M group, respectively). Serious TEAE were observed in 7% of patients and 4% of patients stopped the study after a TEAE. Respectively 5% in the PP3M group and 7% in the PP1M group showed serious TEAEs, such as worsening of the disease. The most common TEAEs observed were increased weight, nasopharyngitis, anxiety and headache (respectively 21%, 7%, 5% and 4% in the PP3M group and 21%, 6%, 5% and 5% in the PP1M group). Both groups presented a similar incidence of EPS and tardive dyskinesia, which were reported in the second and in the third phases (1 patient for each group in each phase). Diabetes mellitus and hyperglycemia-related TEAEs resulted to be lower in the PP3M group than the PP1M group (respectively 2.6% and 4.9%). Weight gain, defined by an increase greater than 7%, was observed in 136 patients in the PP3M group (27%) and in 150 patients in the PP1M group (30%). Increase of prolactin levels were greater in men from PP1M group (45% versus 39% in the PP3M group), while the percentage of hyperprolactinemia in women was similar in both groups (33% in the PP3M group and 32% in the PP1M group, respectively). Considering QTcLD, researchers observed a maximum increase between 30 and 60 milliseconds (10% of patients in the PP3M group and 6% of patients in the PP1M group) and each group presented 1 patient with a maximum increase greater than 60 milliseconds. One patient from the PP1M group presented QT interval value greater than 500 milliseconds based on QTcB, QTcF, QTLc, and QTcLD during the double-blind phase. Other changes in vital signs were similar and, generally, minimal in both groups. A greater rate of injection site-related TEAEs was reported in the PP3M group (8%) compared to the PP1M group (6%). Anyway, the local injection-site tolerability was generally good in both groups (induration, redness and swelling were lower than 5% of patients in both groups). The incidence of agitation and aggressive behavior, somnolence, sedation, tachycardia, orthostatic hypotension were similar in both groups. During the study, 6 patients died, but only 1 of them, in the PP1M group, due to suicide attempt (other death were correlated to arteriosclerosis and cardiac arrest, hepatocellular carcinoma, toxicity to other agents and bacterial meningitides).

PALIPERIDONE PALMITATE ONE MONTHLY VERSUS RISPERIDONE LONG-ACTING INJECTABLE AND OTHER MOLECULES

A number of studies compared PP1M and risperidone long-acting (RIS-LAI) (Table 5).

The first³¹ was a 53-week, double-blind study designed to evaluate the non-inferiority of paliperidone palmitate 1 monthly to risperidone long-acting. The study was divided in a 7-day screening phase and a 53-week double-blind treatment phase. Patients were randomly assigned (1:1) to flexible dosed PP1M + oral placebo (PP1M group) or flexibly dosed RIS-LAI + oral risperidone (RIS-LAI group). From a total of 749 enrolled patients, 339 (45%) of them completed the study. The RIS-LAI group showed an higher completion rate than the PP1M group (50% and 41%, respectively). For

Table 5. Comparison between paliperidone palmitate 1 monthly and risperidone LAI or other long-acting molecules: assessments and main findings.

Authors	Assessment	Main effect of treatment with PP1M
Fleischhacker et al. ³¹	Patients were assigned to PP1M + oral PB (n:379) or RIS-LAI + oral RIS (n:370)	PP1M did not appear non-inferior to RIS at the efficacy measures
Pandina et al. ³²	Patients were randomized to PP1M + oral PB (n:607) or RIS-LAI + oral RIS (n:613)	Compared to RIS, PP1M showed similar improvement in PANSS TS, CGI-S and PSP
Li et al. ³³	Patients were randomized to PP1M (n:229) or RIS-LAI (n:223)	PP1M appeared to be non-inferior to RIS-LAI
McEvoy et al. ³⁶	Patients were randomized to PP1M (n:145) or HD (n:145)	Both groups presented a similar decrease in PANSS total score at each control visit and no significant differences in the rate of efficacy failure were found. Patients from the PP1M group showed a weight gain
Naber et al. ³⁹	Patients were randomized to PP1M 50-150 mg (n:147) or AOM 400 mg (n:148)	Patients in the AOM ones showed significant improvements in CGI-S and IAQ scores, as well as in the Intrapsychic Foundations domain of the QLS. These findings were confirmed in patients younger than 35 years old, while older patients did not presented differences between the two groups. Weight gain, psychotic disorder, and insomnia were more frequent in the PP1M group

AOM: aripiprazole once-monthly HD: haloperidol decanoate; LAI: long-acting injectable; PP1M: paliperidone palmitate 1 monthly; PB: placebo; RIS: risperidone; TS: total score.

the per-protocol analysis set, the mean (SD) change from baseline to endpoint in PANSS total score was -1.6 (21.22) in the PP1M group and -14.4 (19.76) in the RIS-LAI group, while the least-squares mean difference between the two groups for the changes in PANSS total score was -2.6 (95% CI -5.84 to 0.61). As the lower limit of the 95% CI was less than -5, PP1M as dosed in this study was not found non-inferior to risperidone long-acting.

The non-inferiority of PP1M versus risperidone long-acting injectable was evaluated in another 13-week double-blind study³². The study was a randomized, double-blind, double-dummy, active-controlled, parallel-group, multicenter, non-inferiority comparative study. The study consisted of a 7-day screening period followed by a 13-week double-blind treatment period. Eligible patients were randomly assigned (1:1) to the PP1M group (characterized by the absence of an oral supplementation therapy) or RIS-LAI group (with oral risperidone). Of the 1220 patients randomly assigned to one of the treatment groups, 927 (76%) completed the study. For the per-protocol analysis set, both PP1M and RIS-LAI group presented a similar mean (SD) change from baseline in PANSS total score, which resulted to be at the endpoint -18.6 (15.45) and -17.9 (14.24) respectively. The point estimate of the treatment difference of the change in the PANSS total score was 0.4 (95% CI [-1.62, 2.38]) in favor of PP1M, which demonstrated its non-inferiority compared to RIS-LAI. Furthermore, the difference change in PANSS total score was 1.2 (95% CI [-0.78, 3.16]) in favor of PP1M according to per-protocol analysis set, in CGI-S was 0.0 (95% CI: -0.07, 0.17) and in PSP was 0.2 (95% CI: -1.22, 1.69), both according to last observation carried forward difference. Moreover, at the endpoint, 53% of the PP1M group and 48.5% of the RIS-LAI group responded (30% PANSS responder rate) to treatment: the point estimate (95% CI) of the relative risk of

PP1M vs RIS-LAI was 1.1 (0.97, 1.25).

The non-inferiority of PP1M versus risperidone long-acting injectable was evaluated also in another open-label, rater-blinded, parallel-group study³³ in Chinese patients. The study was divided in a 7-day screening phase and a 13-week open-label phase. Eligible patients were randomly assigned (1:1) to the flexibly dosed PP1M treatment group (without any oral supplementation) or to the RIS-LAI treatment group (with oral risperidone supplementation). During the open-label phase, PP1M group patients received injections of paliperidone on day 1 (150 mg eq), on day 8 (100 mg eq) and subsequent once-monthly (50, 100 or 150 mg eq). In the RIS-LAI group, patients received injections of risperidone on day 8 (25 mg) and then every 2 weeks (25, 37.5, or 50 mg). Of the total 452 randomized patients, 350 (77.4%) completed the study. The difference in least square means in PANSS total score change was -5.20 (0.63), considering a 95% CI, and therefore paliperidone palmitate appeared to be non-inferior to RIS-LAI. This result was also confirmed by repeated measure mixed effect model. Results of the exploratory analysis indicated less improvement in PANSS total score but an increase of BMI in the PP1M group, while this trend was not observed in the RIS-LAI group. Similar improvements were seen in both treatment groups for CGI-S, PSP and the PANSS subscale scores and Marder factor scores. At the endpoint, the response to treatment was respectively of 70.7% patients in the PP1M group and 78.4% patients in the RIS-LAI group.

An important difference between RIS-LAI and PP1M, aside from the efficacy and tolerability profile of the two antipsychotic molecules, is represented by the frequency of administration, also known as dosing regimen. The interval of time between two subsequent doses of RIS-LAI is of two weeks, whereas with PP1M it is of 1 month, with the possi-

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bility of extending it to 3 months with PP3M. While closer intervals between administrations allow for a more strict monitoring of response and side effects, longer intervals allow for an even more equal distribution of the drug during time and longer periods of guaranteed pharmacological treatment. Current literature does not show differences in main clinical outcomes between the two approaches, therefore efficacy and tolerability in each clinical case and patient choice and convenience should remain the priority^{34,35}.

A comparison between PP1M and haloperidol decanoate was made in a multisite, parallel-group, double-blinded randomized clinical trial³⁶. The study included an oral trial lasted from 4-7 days, followed by the beginning of the long-acting therapy and a follow-up of 24 months. Eligible patients, including those with a history of medication non-compliance and/or significant substance abuse, were randomly assigned 1:1 to receive PP1M or haloperidol decanoate. From a sample of 311 patients, 290 completed the study (145 patients in each group). During the study, both groups presented a similar decrease in PANSS total score at each control visit, as well as the rates of treatment discontinuation due to any cause or to unacceptable side effects. No significant differences in the rate of efficacy failure were found among the two groups. Furthermore, the incidence of probable tardive dyskinesia and the ratings at the Abnormal Involuntary Movement Scale (AIMS)⁹ and Simpson-Angus Extrapyramidal Scale (SAS)³⁷ global scores appeared similar in the two groups, while the Barnes Akathisia Rating Scale (BARS)³⁸ global score was higher in the haloperidol decanoate group ($p=0.006$). Patients from the PP1M group showed a weight gain, while those in haloperidol lost it ($p=0.03$). Conversely, no differences were observed in the mean change of HbA1c, glucose, triglycerides, total cholesterol, LDL and HDL cholesterol. Both groups showed an increase in prolactin levels, but no differences were found in sexual dysfunction, gynecomastia or galactorrhea.

In another trial, PP1M and aripiprazole once-monthly were compared in 28-week, multicenter, randomized, non-inferiority, open-label, rater-blinded, head-to-head study³⁹. The trial was a phase 3b study in which 295 patients were randomized in the aripiprazole once-monthly (AOM) 400 mg group or in the PP1M 50-150 mg group. Compared to the PP1M group, patients in the AOM ones showed significant improvements at the endpoint in CGI-S and Investigator's

Assessment Questionnaire (IAQ)⁴⁰ scores, as well as in the Intrapyschic Foundations domain of the Heinrichs-Carpenter Quality-of-Life Scale (QLS)⁴¹. These findings were confirmed in patients younger than 35 years old (CGI-S: $p=0.026$; IAQ: $p=0.048$; QLS $p=0.037$), while older patients did not presented differences between the two groups. The most common cause of discontinuation was due to TEAE. Weight gain, psychotic disorder, and insomnia were more frequent in the PP1M group, while the incidence of extrapyramidal symptoms was low and similar among both groups.

ECONOMIC IMPACT

Even if schizophrenia can be considered a rare disorder, it accounts for around 25% of total psychiatric expenditures⁴². This peculiarity is correlated to its early onset, the chronic nature of the disorder and the course, with frequent progressive worsening and high comorbidity. Global spending is subdivided into direct costs related to cure, which represent the lowest proportion, and indirect costs, which are expressions of the effects of the disorder and of the effects on care costs (taking up about 60-65% of costs)⁴³. Studies concerning the pharmacoeconomic aspects of the use of paliperidone palmitate are shown in Table 6.

In a study⁴⁴, researchers retrospectively compared costs and resource utilization among Medicaid schizophrenic patients who were treated with PP1M versus oral antipsychotic therapy. They evaluated the healthcare utilization and costs at the baseline and after a follow-up of 12-months. Patients were selected from the MarketScan Medicaid Multi-State Database and were required to have continuous enrollment 6 months before and 12 months after the start of the study: 984 patients were screened in the PP1M group and 4199 in the oral antipsychotic therapy group. The healthcare costs were identified by type of service and specified as all-cause and mental-health related (e.g. inpatient admissions, emergency department visits, outpatient office visits). Monthly prescription drug costs for the PP1M group were higher than the oral antipsychotic therapy group, both for all-cause pharmacy costs ($p<0.0001$) and mental-health-related costs ($p<0.0001$). Conversely, costs for other components of care were lower in the PP1M group than in the oral antipsychotic therapy group, such as the costs for inpatient services and for outpatient

Table 6. Economic impact: assessments and main findings.

Authors	Assessment	Main effect of treatment with PP1M
Pesa et al. ⁴⁴	The sample was composed by a PP1M cohort (n:984) and a OAT cohort (n:4199)	Compared to OAT, PP1M appeared less expensive in terms of all-cause and mental health related care costs, as well as associated with a lower risk of healthcare resource utilization
Lefebvre et al. ⁴⁵	The sample was composed by a PP1M cohort (n:1684) and a OAT cohort (n:5188)	Compared to OAT, PP1M was associated with all cause medical savings
Pilon et al. ⁴⁷	The sample was composed by a PP1M cohort (n:2053) and a OAA cohort (n:22247)	Compared to OAT, PP1M appeared similar in total healthcare costs; in recently diagnosed group, PP1M appeared more expensive regarding the total pharmacy costs but less in the home care services one

OAA: oral atypical antipsychotic; OAT: oral antipsychotic therapy; PP1M: paliperidone palmitate 1 monthly.

services respectively in terms of all-cause costs (respectively $p=0.0003$ and $p<0.0001$) and costs specific to mental-health-related care ($p<0.0001$ both). Consequently, about 55% of the mental-health-related prescription drug cost premium associated with PP1M was offset by lower costs of mental-health-related inpatient and outpatient care and the mean monthly total cost resulted significantly differential both for all-cause costs and mental-health-related costs (both $p<0.0001$). Furthermore, PP1M was associated with lower risk of healthcare resource utilization compared to oral antipsychotic therapy: in the PP1M group the risk of an inpatient hospital admission and mental-health-related utilization were lower (both $p<0.0001$), as well as the risk of an emergency department visit (all-causes, $p=0.0134$).

In another retrospective longitudinal study in veterans with schizophrenia and comorbid substance abuse⁴⁵, researchers screened patients from the Veterans Health Administration (VHA) electronic health record data. Enrollment in VHA was between 12 months before and 6 months after the index date. Global Assessment of Functioning (GAF)⁴⁶ was measured at baseline. From the index date, all patients were observed for a year to establish health care resource utilization (HRU) and cost outcomes. When follow-up was shorter than a year, outcomes were annualized to 12 months. On the base of their index therapy, patients were assigned to PP1M group or to oral atypical antipsychotic group. The oral atypical antipsychotics included aripiprazole, olanzapine, paliperidone, risperidone, quetiapine, iloperidone, lurasidone, ziprasidone and asenapine. The main outcomes evaluated by researchers were the treatment patterns (such as days of persistence, discontinuation, proportions of days covered by treatment, oral atypical antipsychotic use, concomitant medication use, psychiatric polypharmacy, and antipsychotic polypharmacy), HRU and healthcare costs. Duration of treatment was indicated as the smaller number of days a patient was observed with some supplementary days when necessary. Psychiatric polypharmacy was defined as overlapping coverage of at least 1 antipsychotic agent and at least 1 anxiolytic, antidepressant, or non antipsychotic mood stabilizer for 60 consecutive days or more. All-cause and substance abused-related inpatient and outpatient HRU and costs were assessed and further stratified into relevant categories, such as mental health costs, long-term care costs, other inpatient costs, emergency room costs, mental health intensive case management costs, and other outpatient costs. Inpatient and outpatient visit cost were added to calculate total medical cost. Total medical and pharmacy costs were summed to estimate the total overall costs. PP1M was associated with significant total all-cause medical cost savings compared to oral atypical antipsychotic treatment ($p<0.001$). Though PP1M treatment was associated with more expensive total all-cause outpatient visit costs ($p=0.004$), it was marked by lower total overall inpatient stay costs ($p<0.001$). The two groups did not present differences in the overall all-cause costs ($p=0.084$) due to the higher pharmacy costs associated with PP1M ($p<0.001$). Anyway, PP1M was related to smaller substance abuse-related total medical costs ($p<0.001$), as well as substance abused-related inpatient costs and substance abused-related outpatient costs (respectively $p<0.001$ and $p=0.537$).

In another retrospective longitudinal cohort study⁴⁷ researchers used adult Medicaid data to compare treatment patterns, healthcare resource utilization, and Medicaid spending in patients with diagnosis of schizophrenia who

were treated with PP1M versus oral atypical antipsychotics. Patients had to have at least a year of continuous Medicaid enrollment previously to the index date and to have at least a year of post-index continuous Medicaid enrollment. From the index data, outcomes were evaluated during a fixed 12-month observation period. Treatment groups were defined on the index date by the agent. Main outcomes included treatment patterns (such as the duration of continuous exposure to the index agent, the number of dispensing of the index agent, psychiatric medication use different from the index agent, the presence of antipsychotic polypharmacy and the presence of psychiatric polypharmacy), all-cause healthcare resource utilization and healthcare costs over the 12-month observation period for each patient. Persistence and adherence to treatment were also observed, with patients defined as adherent if they obtained a proportion of days covered greater than 80%. Frequency of visits/services use was evaluated by type to estimate the healthcare resource utilization, while medical costs by type of service and total pharmacy costs to estimate healthcare costs. In the recently diagnosed group, thanks to the lower home care costs ($P<0.001$), PP1M, which is more expensive ($p<0.001$), was associated with lower medical costs ($p=0.028$), resulting in the end in similar total healthcare costs compared to oral atypical antipsychotic ($p=0.553$). In the overall group, medical cost resulted less expensive in PP1M than in the oral atypical antipsychotics group ($p<0.001$), while total healthcare costs were similar in both group ($p=0.709$). Lower inpatient costs ($p<0.001$) and lower home care costs ($p=0.012$) were directly connected to the medical cost savings of PP1M. Anyway, PP1M was characterized by higher total pharmacy costs ($p<0.001$), while total healthcare costs were similar between the two groups ($p=0.533$). In the recently diagnosed patients, PP1M showed a reduction in the cost of home care services ($p=0.008$), while the rates of mental health institute admissions and 1-day mental health institute admissions resulted higher compared to oral atypical antipsychotic (respectively $p=0.044$ and $p=0.028$). Moreover, in the recently diagnosed group, cumulative lengths of stay for all-cause inpatient visits and long-term care admissions appeared shorter in PP1M treatment compared to oral atypical antipsychotic, but without a significant difference (respectively $p=0.353$ and $p=0.060$). Lower rates of long-term care admissions were observed with PP1M treatment ($p<0.001$). Researchers observed 35% fewer long-term care days ($p=0.012$), 22% lower rate of home care visits ($p=0.048$) and 16% fewer all-cause inpatient days ($p=0.004$) associated with PP1M treatment, while rates of mental health institute admissions ($p<0.001$), 1-day mental health institute admissions ($p<0.001$) and cumulative length of stay for mental health institute admissions ($p<0.001$) all resulted to be significantly higher. Even if PP1M patients showed a lower rate of visits or services use, these findings resulted not significant ($P>0.05$) and no significant differences were found considering outpatient or emergency room or inpatient visits, as well as long-term care admissions and other services.

CONCLUSIONS

Considering the above-mentioned studies, we can assume that paliperidone palmitate is a strongly indicated therapeutic

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tic option in the short-term treatment of schizophrenia: data on the changes induced by treatment, in particular on PANSS, CGI-S and PSP scores show a favorable profile of efficacy. As regards the long-term use, the available data indicate that paliperidone palmitate not only allows to maintain the improvement observed in the acute phases of treatment but is also able to induce further improvements both in the symptoms severity and in personal and social functioning. Paliperidone palmitate can also be considered a globally well tolerated compound both in the short- and long-term, as documented by a low incidence of serious adverse events. Furthermore, it is worth noting that the extrapyramidal side effects are rare, the impact on body weight is minimal and there are no significant metabolic index changes. Although increases in prolactin levels were observed, only few patients reported prolactin-related adverse events.

The main limitations of the present review lie in its narrative structure: its findings cannot be considered conclusive as those of a systematic or meta-analytical review and it's possible that a number of studies have not been considered for inclusion. Another possible limitation is that part of the clinical studies included are pre-commercialization studies, which are already widely known by the scientific community.

Compared to first generation LAI antipsychotics, paliperidone palmitate shows an equally valid efficacy profile but better tolerability, especially when considering extrapyramidal side effects. Further studies are required in order to assess its efficacy when directly compared to other second generation LAI antipsychotics; however, current evidences suggest that differences may emerge in collaterality profiles and in particular when considering specific side effects.

In conclusion, the tolerability and efficacy data make paliperidone palmitate a valid option for the short- and long-term treatment of schizophrenia. Moreover, the economic impact of the use of paliperidone palmitate on the health care appears to be advantageous compared to the use of oral antipsychotics, also considering modern, second-generation antipsychotics that can be considered valid treatment options for patients with schizophrenia.

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REFERENCES

1. Nasrallah HA. The case for long-acting antipsychotic agents in the post-CATIE era. *Acta Psychiatr Scand* 2007; 115: 260-7.
2. Valsecchi P, Garozzo A, Nibbio G, et al. Paliperidone extended-release in the short- and long-term treatment of schizophrenia. *Riv Psichiatr* 2019; 54: 43-58.
3. INVEGA SUSTENNA: Highlights of prescribing information. Janssen Pharmaceuticals. Revised: October 2011.
4. Bishara D. Once-monthly paliperidone injection for the treatment of schizophrenia. *Neuropsychiatric Dis Treat* 2010; 6: 561-72.
5. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association, 2000.
6. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association, 2000.
7. Kramer M, Litman R, Hough D, et al. Paliperidone palmitate, a potential long-acting treatment for patients with schizophrenia. Results of a randomized, double-blind, placebo-controlled effi-

- cacy and safety study. *Int J Neuropsychopharmacol* 2010; 13: 635-47.
8. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987; 13: 261-76.
9. Guy W (ed). ECDEU Assessment Manual for Psychopharmacology. Publication ADM 76-338. Washington, DC: US Department of Health, Education, and Welfare, 1976 (pp. 534-7).
10. Gopal S, Hough DW, Xu H, et al. Efficacy and safety of paliperidone palmitate in adult patients with acutely symptomatic schizophrenia: a randomized, double-blind, placebo-controlled, dose-response study. *Int Clin Psychopharmacol* 2010; 25: 247-56.
11. Morosini PL, Magliano L, Brambilla L, Ugolini S, Pioli R. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. *Acta Psychiatr Scand* 2000; 101: 323-9.
12. Pandina GJ, Lindenmayer JP, Lull J, et al. A randomized, placebo-controlled study to assess the efficacy and safety of 3 doses of paliperidone palmitate in adult with acutely exacerbated schizophrenia. *J Clin Psychopharmacol* 2010; 30: 235-44.
13. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. *J Clin Psychiatry* 1997; 58: 538-46.
14. Nasrallah HA, Gopal S, Gassmann-Mayer C, et al. A controlled, evidence-based trial of paliperidone palmitate, a long-acting injectable antipsychotic, in schizophrenia. *Neuropsychopharmacology* 2010; 35: 2072-82.
15. Hargarter L, Cherubin P, Bergmans P, et al. Intramuscular long-acting paliperidone palmitate in acute patients with schizophrenia unsuccessfully treated with oral antipsychotics. *Prog Neuropsychopharmacol Biol Psychiatry* 2015; 58: 1-7.
16. Linden M, Stefanie B. Das "Mini-ICF-Rating für psychische Störungen (Mini-ICF-P)". Ein Kurzinstrument zur Beurteilung von Fähigkeitsstörungen bei psychischen Erkrankungen (The Mini-ICF-rating for mental disorders (Mini-ICF-P)). *Die Rehabilitation (Stuttg)* 2005; 44: 144-51.
17. Naber D, Moritz S, Lambert M, et al. Improvement of schizophrenic patients' subjective wellbeing under atypical antipsychotic drugs. *Schizophr Res* 2001; 50: 79-88.
18. Atkinson MJ, Sinha A, Hass SL, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. *Health Qual Life Outcomes* 2004; 2: 12.
19. Chouinard G, Margolese HC. Manual for the Extrapyramidal Symptom Rating Scale (ESRS). *Schizophr Res* 2005; 76: 247-65.
20. Kwon JS, Kim SN, Han J, et al. Satisfaction of immediate or delayed switch to paliperidone palmitate in patients unsatisfied with current oral atypical antipsychotics. *Int Clin Psychopharmacol* 2015; 30: 320-8.
21. Kalali A. Patient satisfaction with, and acceptability of, atypical antipsychotics. *Curr Med Res Opin* 1999; 15: 135-7.
22. Kalali AH. Evaluating patient satisfaction: a practical approach. *Clear Perspectives* 1999; 2: 18-21.
23. Si T, Zhang K, Tang J, et al. Efficacy and safety of flexibly dosed paliperidone palmitate in Chinese patients with acute schizophrenia: an open-label, single-arm, prospective, interventional study. *Neuropsychiatric Dis Treat* 2015; 11: 1483-92.
24. Thompson K, Kulkarni J, Sergejew AA. Reliability and validity of a new Medication Adherence Rating Scale (MARS) for the psychoses. *Schizophr Res* 2000; 42: 241-7.
25. Schreiner A, Bergmans P, Cherubin P, Hargarter L. The effect of long-acting paliperidone palmitate once-monthly on negative and depressive symptoms in patients with schizophrenia switched from previous unsuccessful treatment with oral aripiprazole. *Ther Adv Psychopharmacol* 2017; 7: 59-65.

26. Hough D, Gopal S, Vijapurkar U, Lim P, Morozova M, Eerdekens M. Paliperidone palmitate maintenance treatment in delaying the time-to-relapse in patients with schizophrenia: a randomized, double-blind, placebo-controlled study. *Schizophr Res* 2010; 116: 107-17.
27. Gopal S, Vijapurkar U, Lim P, Morozova M, Eerdekens M, Houh D. A 52-week open-label study of the safety and tolerability of paliperidone palmitate in patients with schizophrenia. *J Psychopharmacol* 2010; 25: 685-97.
28. Ravenstijn P, Remmerie B, Savitz A, et al. Pharmacokinetics, safety and tolerability of paliperidone palmitate 3-month formulation in patients with schizophrenia: a phase-1, single-dose, randomized, open-label study. *J Clin Pharmacol* 2016; 56: 330-9.
29. Savitz AJ, Xu H, Gopal S, et al. Efficacy and safety of paliperidone palmitate 3-month formulation for patients with schizophrenia: a randomized, multicenter, double-blind, non inferiority study. *Int J Neuropsychopharmacol* 2016; 19: 1-14.
30. Csernansky JG, Mahmoud R, Brenner R; Risperidone-USA-79 Study Group. A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. *N Engl J Med* 2002; 346: 16-22.
31. Fleischhacker WW, Gopal S, Lane R, et al. A randomized trial of paliperidone palmitate and risperidone long-acting injectable in schizophrenia. *Int J Neuropsychopharmacol* 2012; 15: 107-18.
32. Pandina G, Lane R, Gopal S, et al. A double-blind study of paliperidone palmitate and rispridone long-acting injectable in adults with schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2011; 35: 218-26.
33. Li H, Rui Q, Ning X, Xu H, Gu N. A comparative study of paliperidone palmitate and rispridone long-acting injectable therapy in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2011; 35: 1002-8.
34. Kisely S, Sawyer E, Robinson G, Siskind D. A systematic review and meta-analysis of the effect of depot antipsychotic frequency on compliance and outcome. *Schizophr Res* 2015; 166: 178-86.
35. Ting E, Kamalvand S, Shang D, Siskind D, Kisely S. Does the frequency of administration of long acting injectable antipsychotics impact psychiatric outcomes and adverse effects: a systematic review and meta-analysis. *J Psychiatr Res* 2019; 109: 193-201.
36. McEvoy JP, Byerly M, Hamer RM, et al. Effectiveness of paliperidone palmitate vs. haloperidol decanoate for maintenance treatment of schizophrenia: a randomized clinical trial. *JAMA* 2014; 311: 1978-87.
37. Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand* 1970; 212 (suppl): 11-9.
38. Barnes TR. A rating scale for drug-induced akathisia. *Br J Psychiatry* 1989 May; 154: 672-6.
39. Naber D, Hansen K, Forray C, et al. Qualify: a randomized head-to-head study of aripiprazole once-monthly and paliperidone palmitate in the treatment of schizophrenia. *Schizophr Res* 2015; 168: 498-504.
40. Tandon R, Devellis RF, Han J, et al. Validation of the investigator's Assessment Questionnaire: a new clinical tool for relative assessment of response to antipsychotics in patients with schizophrenia and schizoaffective disorder. *Psychiatry Res* 2005; 136: 211-21.
41. Heinrichs DW, Hanlon TE, Carpenter WT. The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. *Schizophr Bull* 1984; 10: 388-98.
42. Rice DP. The economic impact of schizophrenia. *J Clin Psychiatry* 1999; 60 Suppl 1: 4-6; discussion 28-30.
43. Goeree R, O'Brien BJ, Goering P, et al. The economic burden of schizophrenia in Canada. *Can J Psychiatry* 1999; 44: 464-72.
44. Pesa JA, Muser E, Montejano LB, Smith DM, Meyers O. Costs and resource utilization among medicaid patients with schizophrenia treated with paliperidone palmitate or oral atypical antipsychotics. *Drugs Real World Outcomes* 2015; 2: 377-85.
45. Lefebvre P, Muser E, Joshi K, et al. Impact of paliperidone palmitate versus oral atypical antipsychotics on health care resource use and costs in veterans with schizophrenia and comorbid substance abuse. *Clin Ther* 2017; 39: 1380-95.
46. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*. Washington, DC: American Psychiatric Association, 1987.
47. Pilon D, Muser E, Lefebvre P, Kamstra R, Emond B, Joshi K. Adherence, healthcare resource utilization and Medicaid spending associated with once-monthly paliperidone palmitate versus oral atypical antipsychotic treatment among adults recently diagnosed with schizophrenia. *BMC Psychiatry* 2017; 17: 207.