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# Role of 3 monthly long-acting injectable Paliperidone in the maintenance of Schizophrenia

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## Abstract

**Aims:** paliperidone palmitate 3 month (PP3M) represents a new long-acting injectable antipsychotic therapeutic option. This review aims: 1) to summarize available data relating to efficacy, safety, tolerability and costs of PP3M; 2) to describe hospitalization rate, occupational status, treatment preference, satisfaction, adherence and caregiver burden of patients with Schizophrenia who participate to PP3M clinical trials; 3) to examine ethical implications, pros and cons of PP3M use; 4) to propose study designs to further assess PP3M.

**Method:** on August 21, 2017 a search on PubMed about PPM3, without any filter restriction, was conducted and all available records were analyzed. Records written in a language other than English were excluded.

**Results:** 22 records were included in this review: 6 reviews, 1 report, 4 pharmacokinetic (PK) studies, 2 cost-effectiveness analyses, 1 open clinical trial (OCT), 2 randomized clinical trials (RCT), 5 studies based on these two RCTs and 1 observational study.

**Discussion:** according to these last nine studies, when compared to placebo, PP3M showed a longer time to relapse and good safety and tolerability profiles. Furthermore, when compared to paliperidone palmitate 1 month (PP1M), PP3M treatment showed: 1) non-inferiority in terms of efficacy, safety, tolerability, rate of hospitalization, symptomatic and functional remission, treatment preference and variations of the occupational status; 2) a longer time to relapse after treatment discontinuation; 3) a similar reduction of the caregiver burden.

**Conclusion:** PP3M is the only three-monthly LAI antipsychotic available on the market. This makes it a unique option of treatment, which could be chosen both in early and advanced phases of illness. Nonetheless longer naturalistic follow-up studies, two-arm head-to-head superiority trials and mirror studies, based on real-world samples of patients, are needed to further assess long-term safety and advantages of this new option of treatment and to define patients' sub-populations that would most beneficiate from it.

**Keywords:** PP3M, paliperidone palmitate, long-acting antipsychotics, schizophrenia, efficacy, safety

**Running header:** Role of 3 monthly paliperidone in Schizophrenia

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## **Introduction**

Schizophrenia is a pervasive psychotic chronic condition, present in all cultures and historical periods.<sup>1</sup> It is one of the top 20 causes of disability worldwide:<sup>2</sup> World Health Organization (WHO) reported that schizophrenia is responsible for 1.1% of the total disability adjusted life years (DALYs) and 2.8% of the years lived with disability (YLDs).<sup>3</sup> It has an important impact on patients' quality of life and mortality, on patients' families and on social and financial costs:<sup>1,4,5</sup> in developed countries the disorder justifies 1.5-3.0% of healthcare expenses.<sup>6</sup>

Schizophrenia has a prevalence estimated at 0.6 - 0.8% and its lifetime prevalence is about 1% worldwide.<sup>1</sup> Typically it is preceded by prodromal symptoms leading to a first psychotic episode starting in young adulthood.<sup>5,7</sup> Individuals with schizophrenia have a shorter life expectancy than the general population, an increased risk of physical illness, especially cardiovascular disease, as well as higher rates of suicide and accidental injury.<sup>5,7,8</sup> Episodes of partial or full remission broken by relapses characterize the long-term course of schizophrenia as well as difficulties in global functioning:<sup>5,9</sup> most patients are unable to reach at least one milestone, such as being in a stable relationship, having full-time competitive employment, or having self-supported independent living.<sup>10</sup> Relapse in schizophrenia can be destructive often resulting in hospitalization.<sup>11-13</sup> In addition, relapse can be strictly connected with a biological risk: it has been hypothesized that active psychosis reflects a period of disease progression to the extent that patients may not come back to their previous level of functioning and can become resistant to treatment.<sup>14,15</sup> The early phase of schizophrenia, including the first 2 years up to 5 years after the onset, is thought to be essential in determining long-term prognosis.<sup>16</sup> Therefore a continued treatment from the early phases of disease may preserve from structural brain changes and progression towards functional deterioration.<sup>17-20</sup>

## **Poor adherence to treatment and Long Acting Injectable (LAI) atypical antipsychotics**

Antipsychotic therapy is the mainstay of schizophrenia treatment and severity and frequency of disease symptoms can be adequately managed by adhering to the prescribed antipsychotic medication.<sup>5,21,22</sup> The most frequent cause of relapse in schizophrenia is poor adherence to antipsychotic treatment.<sup>23,24</sup> When patients discontinue their medications, even after the first episode, the risk for symptomatic relapse increases dramatically.<sup>25</sup> In clinical settings, poor compliance is common, especially in the early stages of the disease,<sup>26-29</sup> with between 40% and 60% of patients with schizophrenia partially or totally noncompliant with oral antipsychotics.<sup>30,31</sup> It has been highlighted that up to 74% of people affected by schizophrenia started to discontinue their medications after 18 months and that up to 42% of patients stopped their therapy within 1 year after the first psychotic episode.<sup>32,33</sup> Studies using more strict measurement methodology, such as pill count, electronic monitoring, and blood drug level, often indicate higher levels of non-adherence.<sup>34-37</sup> Moreover, the duration of follow-up certainly has a clear influence on the observed frequencies of non-adherence. Therefore, it is reasonable to consider that adherence is much lower in routine care than in clinical trials.<sup>38</sup> Poor adherence has serious repercussions on the course of the disease in terms of relapses.<sup>39,40</sup> Once illness recurrence occurs, the severity of symptoms rapidly returns to levels similar to the initial psychotic episode<sup>25</sup>. This leads to important consequences: inability to work and hospitalization in about 70% of the cases, attempt to suicide in about 20% of the patients, worsening of caregivers' quality of life and higher healthcare-related and indirect costs.<sup>39,40,41</sup> Furthermore, relapses can result in poorer long-term outcomes,<sup>42</sup> such as disease progression and emergent treatment refractoriness.<sup>43,44</sup>

Long-acting injectable (LAI) antipsychotics were developed in order to limit both hidden and overt non-adherence to antipsychotic drugs. LAIs has some known disadvantages as pain on the injection site, lack of flexibility in dose adjustments and patients' perception of stigma and coercion.<sup>40</sup> On the opposite, they have potential advantages like complete tracking of the drug consumption and full adherence in early stages of the disease.<sup>45,46</sup> In addition, LAIs don't need daily administration, which may be perceived by patients as a practical advantage, and minimize the risk of harmful drug use.<sup>47,48</sup> It has also been suggested that pharmacokinetic (PK) differences associated with the route of administration may be a possible advantage for LAI over oral formulations. The higher bioavailability of LAI formulations may help identify the lower effective dose, reducing unnecessary toxic serum levels of the drug.<sup>49</sup> Further, a reduced fluctuation of serum drug levels, and therefore a more stable receptor occupancy,<sup>50</sup> may reduce adverse events (AEs).<sup>49,51</sup> Moreover, in case of sudden treatment interruption, plasmatic drug levels would decrease abruptly. On the contrary, after the discontinuance of the treatment, LAI antipsychotics assure a progressive decrease of the plasma drug levels. This difference might

lower the risk of the so-called “super-sensitivity psychosis”, a severe disease relapse triggered by sudden antipsychotic withdrawal.<sup>52</sup> Furthermore, LAIs facilitate the regular contact between patients and physician and allow physicians to rule out non-adherence as a cause of relapse. At last, should a patient miss an injection, there remains some time to act to avert a crisis.<sup>53</sup>

Among LAIs, second-generation long acting antipsychotics (SGA-LAIs) combine the advantages of second-generation antipsychotics (SGA) with a long-acting formulation.<sup>10</sup> The SGA-LAIs available on the market are: Risperidone LAI (RLAI), Olanzapine LAI (OLAI), Aripiprazole long acting One Month (AOM) and Paliperidone Palmitate (PP) long acting 1-Month (PP1M) and 3-Months (PP3M). Scientific evidence about superiority of SGA-LAIs to SGA oral formulations is controversial. On one hand, randomized controlled trials (RCT), considered to be the ‘gold standard’ for clinical trial design do not support the clinical viewpoint that LAI antipsychotics are generally superior to oral formulations in terms of effectiveness, safety, and tolerability. On the other hand, observational studies (eg cohort and mirror studies), that encompass the concept of effectiveness in a naturalistic-pragmatic setting (more representative of real-life clinical practice), show a greater benefit of LAIs over oral antipsychotics.<sup>54-57</sup> RCTs have high internal validity and allow specific signal detection in carefully selected patient population. Moreover, randomization and blinding of the RCTs can adequately control confounding effects. However, RCTs are frequently affected by selection bias, so they have limited external validity and generalizability to a wider clinical patient population.<sup>56</sup> Observational naturalistic studies analyze real-world patients, limiting selection bias and improving generalizability and external validity. Also, they include pragmatic outcomes such as hospitalizations and all-cause treatment discontinuation. Nevertheless, this kind of study design can be confounded by factors that vary over time and, without a separate control group, this type of confounding cannot be controlled for.<sup>56</sup> Therefore, in order to answer questions of clinical efficacy and effectiveness of LAIs in the range of patients generally seen during routine clinical practice, both RCTs and naturalistic studies are required.<sup>57</sup> About this topic, a recent meta-analysis of head-to-head RCTs comparing the principal SGA-LAIs and their oral counterparts highlighted that: high quality evidence suggests that AOM may provide some small advantages compared to its oral preparation; moderate quality evidence showed that there is no clinical benefit for RLAI; evidence for OLAI was imprecise and therefore not able to rule out neither clinically meaningful superiority, nor inferiority versus oral olanzapine; no evidence for PP was available in July 2016.<sup>54</sup> In order to achieve stronger evidence and recommendations about the use of SGA-LAIs more head to head comparisons between drugs are expected,<sup>57</sup> such as the European Long-acting Antipsychotics in Schizophrenia Trial, which compares oral and LAI formulations of aripiprazole and paliperidone (EULAST; NCT02146547). These

investigations will provide data for further meta-analytic approaches regarding the relative usefulness of the different drugs and formulations available. Future research and experiences will also help to identify which clinical subpopulation may obtain greater benefit from these new formulations, not only in controlling symptoms, but also in terms of cognitive performance, functioning, and quality of life.<sup>58</sup>

## Methods

On August 21, 2017, an electronic search on PubMed about PP3M, without any filter or MESH restriction, was performed, using the following search string: ("3 months" OR "three months" OR "3 monthly" OR "three monthly" OR "3-month" OR "three-month" OR "3-monthly" OR "three-monthly") AND "paliperidone". The query translation of PubMed search engine was as follows: ("3 months"[All Fields] OR "three months"[All Fields] OR "3 monthly"[All Fields] OR "three monthly"[All Fields] OR "3-month"[All Fields] OR "three-month"[All Fields] OR "3-monthly"[All Fields] OR "three-monthly"[All Fields]) AND "paliperidone"[All Fields].

This string was developed because, in scientific literature, PP3M is called in different ways. In particular, the words "three months" (3M) of PP3M, have many different spellings, listed in the proposed string. These spelling were connected by "OR" logical operator. This string guaranteed a high sensitive search, limiting spelling selection of published works indexed in PubMed. Furthermore, an "AND" logical operator was employed to connect these equivalent spellings of 3M with the word "paliperidone" of PP3M. This logical connective led to a high specific search that selected mostly works on topic.

All kinds of publications (i.e. original contributions and reviews) were included. Publications must concern PP3M as principal issue. Publications written in a language other than English were excluded.

## Results

The search described in the previous section provided 38 records. Among them 16 were excluded: 13 because did not concern PP3M and 3 because were not written in English. Thus, this review included 22 records indexed on PubMed: 6 reviews, 1 report, 4 PK studies, 2 cost-effectiveness analyses, 1 open clinical trial (OCT), 2 double blind (DB) RCTs, 5 studies based on these two RCTs and 1 observational study. The selection process and a schematic representation of the results are represented in the literature search flowchart (Figure 1).

**FIGURE 1:** Literature search flowchart

This review will describe the main findings relating to the formulation, pharmacodynamics, PK, safety, tolerability, and efficacy of PP3M, followed by a brief presentation about practical issues encountered with this new formulation. In addition, an overview of possible advantages and disadvantages of PP3M compared with PP1M will be reported. In the final part of this review, PP3M place in therapy and proposals of study designs to further assess this LAI formulation will be discussed. The OCT, the two RCTs, the five articles based on the RCTs and the observational study are summarized in Table 1.

**TABLE 1:** Summary of the clinical studies on PP3M

The OCT was a Phase 1, single dose, randomized, open label study, conducted to investigate the PK, the safety, and the tolerability of PP3M in patients with schizophrenia.<sup>66</sup> The first RCT compared PP3M to placebo in order to assess efficacy and safety of PP3M.<sup>67</sup> The second RCT aimed to demonstrate non-inferiority of PP3M compared with PP1M in terms of relapse rates, changes in Positive and Negative Syndrome Scale (PANSS) scores, Clinical Global Impression-Severity (CGI-S) score and Personal and Social Performance (PSP) score.<sup>68</sup> Savitz et al.,<sup>69</sup> Katz et al.,<sup>70</sup> Chirila et al.<sup>71</sup> and Gopal et al.<sup>72</sup> studied outcome measures within the samples or sub-samples of the two previously described RCTs. In details: Savitz et al.<sup>69</sup> analyzed data derived from the previously mentioned non-inferiority RCT comparing PP3M to PP1M treatment, to investigate symptomatic and functional remission in the DB phase of this RCT, Katz et al.<sup>70</sup> investigated native English-speaking trial participants' and English speaking investigators' judgments about paliperidone formulations and adherence, Chirila et al.<sup>71</sup> compared occupational status and health care resource use between treatment groups (PP3M vs placebo & PP3M vs PP1M), using data from the whole samples of the two RCTs and Gopal et al.<sup>72</sup> evaluated caregiver burden in the two RCTs. Weiden et al.<sup>73</sup> made a post-hoc analysis comparing median time to relapse across the treatment-withdrawal arms of three different RCTs (Kramer et al.,<sup>74</sup> Hough et al.<sup>75</sup> and Berwaerts et al.<sup>67</sup>), which compares the three formulations of paliperidone with placebo. Joshi et al.<sup>76</sup> performed an observational retrospective cohort study, using pharmacy and medical claims data of the Symphony Health Solutions database from May 2014 to September 2017. This study described baseline characteristics and treatment patterns of patients with schizophrenia initiated on PP3M in a real-world setting in the USA.

## Discussion

### ***Overview of pharmacology, pharmacokinetics of Paliperidone palmitate 3 monthly injection***

**Formulation properties** PP3M contains a racemic mixture of the active ingredient paliperidone (9-OH risperidone), an atypical antipsychotic belonging to the chemical class of benzisoxazole derivatives, derived from risperidone.<sup>77,78</sup> PP is the palmitate salt ester of paliperidone. PP is very slightly soluble in polar solvent.<sup>77,78</sup> Tiny drug crystals are created and dispersed in an aqueous suspension (NanoCrystal technology). These crystals are nanoparticles, usually defined as having a size between 1–1,000 nm. These tiny drug crystals are dispersed in an aqueous suspension (nanosuspensions), that is the LAI formulation of PP.<sup>79</sup> The PP3M formulation utilizes NanoCrystal technology similar to the PP1M but with increased particle size, allowing an extended sustained release.<sup>66</sup> These nanoparticles dissolve slowly after intramuscular (IM) injection before being hydrolyzed to paliperidone by the esterases present in muscle tissue. Then paliperidone diffuses into the systemic circulation.<sup>79,80</sup> PP3M is available in dose strengths of 273 mg, 410 mg, 546 mg, and 819 mg paliperidone palmitate, that undergo hydrolysis resulting in dose strengths of 175 mg, 263 mg, 350 mg, and 525 mg of paliperidone, respectively.<sup>79</sup>

#### **Pharmacodynamics**

Therapeutic efficacy of paliperidone likely occurs through its antagonism of both central dopamine D2 and serotonin 5-HT<sub>2A</sub> receptors. Plasma concentrations of 10–17 ng/mL were estimated to correspond to 70–80 % occupancy of D2 receptors.<sup>81</sup> A D2 receptor occupancy of 65–80 % is generally considered optimal, with levels exceeding this conferring an increased risk of extrapyramidal symptoms.<sup>82</sup> Paliperidone is also an antagonist at  $\alpha$ <sub>1</sub>- and  $\alpha$ <sub>2</sub>- adrenergic receptors and H<sub>1</sub> histaminergic receptors.<sup>82,83</sup> This activity profile of paliperidone may explain some of the potential adverse effects of the drug, such as orthostatic hypotension and weight gain.<sup>83</sup> A difference of risperidone's mechanism of action, paliperidone does not block beta adrenoceptors, muscarinic cholinceptors or peptidergic receptors.<sup>77</sup>

#### **Pharmacokinetics (PK)**

Nanoparticles of PP3M dissolve slowly after IM injection; release starts as early as day 1 and lasts for up to 18 months.<sup>79</sup> The paliperidone plasma concentration-time profiles for the corresponding PP1M and PP3M doses are similar. The principal differences concern the pre-dose plasma concentrations of PP3M: they are 21% lower than the concentrations observed



following PP1M administration. Mean peak-to-trough ratios are higher following PP3M administration (range: 1.86–2.54) than PP1M administration (range: 1.30–1.63).<sup>66</sup> With regard to metabolism and elimination, information from studies of oral paliperidone are reported: approximately 59% of a single dose of the drug is excreted unchanged in the urine; approximately 80% of the radioactivity related to a single oral dose of <sup>14</sup>C paliperidone is recovered in the urine and 11% in the feces, indicating a lack of extensive hepatic metabolism.<sup>77</sup> Results obtained in *in vitro* studies suggest that CYP2D6 and CYP3A4 may be implicated in the metabolism of paliperidone, although no evidence of their role derive from *in vivo* studies: inhibitors or inducers of CYP2D6 and CYP3A4 do not significantly influence paliperidone plasma levels and no significant induction or inhibitory properties of paliperidone on the cytochrome system have been demonstrated.<sup>66</sup>

**Dosing and switching** PP3M injections should be started at a dose 3.5-fold multiple of the preceding dose of PP1M, and administered in either the deltoid or the gluteal muscle at the time scheduled for the next PP1M dose.<sup>79</sup> Available marketed doses are listed in Table 2.

**TABLE 2.** Conversion between PP1M and PP3M doses. (Gopal 2015)<sup>79</sup>

Treatment with PP3M should only be initiated in patients who had adequately responded to and tolerated treatment with PP1M for at least 4 months.<sup>79</sup> Due to the slow release profile, treatment with PP3M is not indicated for use in acutely symptomatic patients or in patients who are transitioning from oral or other, non-PP1M, LAI antipsychotic therapy.<sup>79</sup> It is recommended that the last two PP1M doses prior to switching to PP3M are the same and patients are supposed to be clinically stable at the end of the PP1M dosing before transitioning to PP3M.<sup>79</sup> According to PK simulations, during maintenance therapy of PP3M, changes in plasma concentrations allow a flexible dosing window of 2 weeks for regularly scheduled 3 monthly injections.<sup>79</sup>

**TABLE 3.** Management of missed PP3M injections (adapted from Gopal 2015)<sup>79</sup>

**PP3M injection procedure** One significant difference between the preparation of PP1M and PP3M is the force of shaking required to re-suspend the syringe contents. The PP3M syringe must be shaken vigorously for at least 15 seconds with a loose wrist before injecting the formulation to ensure a homogenous suspension. Improper shaking could result in clumping, and inability to express the entire medication content from the syringe barrel.<sup>79</sup> Furthermore, a suitable syringe must be used: in the RCT comparing PP3M and PP1M, the use of a shorter syringe and the consequent lower dose administration of PP3M caused the exclusion of some patients from the study.<sup>68,69</sup>

## ***Clinical efficacy, safety and tolerability of PP for Schizophrenia***

**Efficacy and hospitalization rate** Efficacy of PP3M was evaluated against placebo<sup>67</sup> and in terms of non-inferiority against PP1M<sup>68</sup> in two different DB RCTs summarized in Table 1. The first study was stopped by an independent data monitoring committee for greater efficacy of PP3M compared to placebo: during the DB phase, 29% of patients in the placebo group experienced a relapse event against 9% in the group receiving PP3M.<sup>67</sup> The final data analysis included 305 patients (PP3M: n = 160; placebo: n = 145) and showed superiority of PP3M over placebo in delaying time to relapse of schizophrenia symptoms ( $P < .001$ ; hazard ratio = 3.81; 95% CI, 2.08-6.99), a result confirmed by Cox proportional hazards models.<sup>67</sup> Furthermore, Weiden et al. post-hoc study<sup>73</sup> showed longer time to relapse after PP3M treatment discontinuation compared to that of oral paliperidone and PP1M: in particular, after suspension of the treatment, 50% of patient treated with PP3M remained relapse free for approximately 13 months, instead of 6 months with PP1M treatment withdrawal. Also, according to this study, the relapse risk (hazard ratio) was 2.08 higher for patients discontinuing PP1M than for those discontinuing PP3M.<sup>73</sup> However, as these data come from a descriptive post-hoc analysis and not a meta-analysis of the datasets of the three different RCTs (Kramer et al.,<sup>74</sup> Hough et al.<sup>75</sup> and Berwaerts et al.<sup>67</sup>), caution must be used when interpreting this study. Furthermore, this was not a head-to-head discontinuation RCT comparing oral paliperidone, PP1M and PP3M in the same trial, therefore, the evidence of this post-hoc analysis has strong study-design and generalizability limitations.

The non-inferiority phase-3 RCT<sup>68</sup> demonstrated that PP3M treated group had relapse rates similar to PPM1 treated group, based on Kaplan-Meier estimates. Variations from DB baseline in positive and negative symptom scale (PANSS) total score and subscale scores, in Clinical Global Impression-Severity (CGI-S), and in Personal and Social Performance (PSP) scores were similar in the two experimental groups.<sup>68</sup> Furthermore, PP3M and PP1M treatments showed comparable symptomatic (defined according to Andreasen's criteria on PANSS) and functional remissions (PSP > 70) during the last six months of DB phase. In addition, most patients who achieved remission at DB baseline maintained their remission status throughout the DB phase.<sup>69</sup>

Moreover, healthcare resource use was studied in the two described RCTs<sup>67,68</sup> in terms of hospitalization odds.<sup>71</sup> The placebo group showed a higher rate of hospitalization for either psychiatric and social reasons or for social reason alone compared to PP3M.<sup>71</sup> No difference in terms of hospitalizations was observed between PP3M and PP1M groups.<sup>71</sup>

### **Safety and tolerability**

Safety and tolerability were examined in the two previously described RCTs and in the phase-1 OCT.<sup>66</sup> This latter one showed that headache and nasopharyngitis were the most common (>7%) treatment-emergent adverse events (TEAEs) and described a safety and tolerability profile similar to those of PP1M.<sup>66</sup> Compared with placebo, PP3M treatment demonstrated a similar proportion on TEAEs developed during the DB phase of the study: 62% of the subjects treated with PP3M injections and 58% on the subject that received placebo injections had at least one TEAE. TEAEs noted more frequently in the group receiving PP3M than in the placebo group were headache (9% vs 4%), weight increase (9% vs 3%), nasopharyngitis (6%vs 1%), and akathisia (4%vs 1%).<sup>67</sup> In the non-inferiority phase-3 RCT safety and tolerability profiles of PP3M and PP1M were comparable over the whole DB phase of the study. Withdrawal rates due to TEAEs were low and comparable for both treatments.<sup>68</sup> Serious TEAEs were mostly of a psychiatric nature and similar between both groups.<sup>68</sup> Weight gain, nasopharyngitis, and anxiety were the most common TEAEs in both groups.<sup>68</sup> Other TEAEs like EPS, suicidality, agitation and aggression, somnolence and sedation, tachycardia, orthostatic hypotension, QTc interval prolongation, potentially prolactin-related, and weight gain-related TEAEs had a similar frequency in the two experimental groups.<sup>68</sup>

### **Pregnancy**

With its release during 18 months from the injection, PP3M makes more likely fetal exposition to paliperidone. However, few data about paliperidone effects in pregnancy are available in scientific literature. Two case reports of women in treatment with PP1M during pregnancy reported no congenital malformation and no perinatal complications of the newborns.<sup>84,85</sup>

## ***Other features of PP3M and ethical implications***

### **Quality of life, satisfaction, adherence**

To our knowledge, no studies about quality of life, satisfaction, and adherence of PP3M treated patients with schizophrenia have been performed, yet. Longer follow-up studies should be carried out in order to compare switching from PP1M to PP3M treatment.

### **Caregiver burden**

Gopal et al.<sup>72</sup> study showed that switching from an oral antipsychotic to either PP1M or PP3M can significantly reduce caregiver burden. This mirror image study was performed on data derived from the non-inferiority phase-3 RCT comparing PP1M and PP3M.<sup>68</sup> For this reason both treatments groups received a monthly injection and caregiver burden reduction due to diminished number of administrations was not detectable.<sup>72</sup> To our knowledge, no studies on this topic in the transition from PP1M to PP3M in a real-world setting are available.

### **Antipsychotic preference according to formulation**

Katz et al.<sup>70</sup> analyzed preferences between oral antipsychotic treatments, PP1M, and PP3M with a survey performed by English native speaking and English-speaking physicians who participated in the two RCTs<sup>67,68</sup> previously described.

According to this study patients and physicians preferred LAIs over oral antipsychotics and were willing to accept reduced efficacy in exchange for switching from an oral formulation to a LAI. Physicians showed a greater preference for 3-month over 1-month LAI.<sup>70</sup>

#### **Occupational status variation**

Chirila et al.<sup>71</sup> described the occupational status of patients who participated in the two RCTs<sup>67,68</sup> previously described. According to that study, no significant differences in terms of variation of the occupational status were observed between PP3M and placebo and PP3M and PP1M treatment, probably because of the short time of follow-up and consequently the small number of patients that changed their occupational status during the two trials.<sup>71</sup> Even if not statistically significant, at the end of the follow-up period (from week 41 until week 53) improvement from baseline in occupational status was slightly higher in the PP3M than in the PP1M group.<sup>71</sup>

#### **Ethical implications**

Both the RCT comparing PP3M with placebo<sup>67</sup> and the RCT comparing PP3M with PP1M<sup>68</sup> were conducted in compliance with the Declaration of Helsinki, consistent with Good Clinical Practices and applicable regulatory requirements and with the approval of independent ethical committees of the participant center. Nonetheless, some ethical critics were made against these studies. First of all, comparing a new drug with placebo might be considered ethically debatable and clinically irrelevant when effective agents are available.<sup>86</sup> In this particular case, the European Medicines Agency (EMA) pointed out the relevance of placebo-controlled studies when assessing the efficacy of new LAIs, arguing that recent schizophrenia trials showed only minimal differences between active treatments and placebo, and therefore an assessment of the absolute effect is required to establish efficacy.<sup>87</sup> With reference to the study comparing PP3M and PP1M it has been pointed out that, as there is no validated and shared method of choice of the non-inferiority margin, the demonstration of non-inferiority leaves uncertainty on whether the two drugs are really equivalent and does not establish whether the new drug tested is associated with additional benefits over the control.<sup>86</sup>

### ***Advantages and disadvantages of PP3M compared with PP1M***

Advantages and disadvantages of PP3M, compared with PP1M treatment, are summarized in Figure 2.

**FIGURE 2** Comparison between PP3M and PPM1 – Pros & Cons

One of the most positive features of PP3M is notable that patients need to receive an injection just four times per year. The lower number of injections is more comfortable for patients, especially for those patients who cannot easily reach the place of administration. Furthermore, less time is needed for drug administration so that saved time and resources can be available for other therapeutic activities, eg rehabilitation. At the same time, psychiatric services with poor human resources, should control the risk to visit the patient exclusively four times a year, on the day of PP3M administration and not according to the health needs of the patient. In terms of costs, three doses of PP1M cost as much as the equivalent dose of one PP3M injection, but the administration costs are reduced to one third. Moreover, two economic studies evaluated cost-utility and cost-effectiveness simulations on the use of PP3M in Spain and in the Netherlands.<sup>88,89</sup> According to these studies, PP3M resulted to be cost-effective for treating chronic schizophrenia and dominated PP1M in all analyses.<sup>88,89</sup>

Finally, PP3M administration protocol admits more flexible delays in PP3M injections interval compared with PP1M. In fact, according to PP3M administration regimen, two weeks of delays after three planned months of inter-injections interval can be tolerated instead of one week with PP1M.

The main disadvantages of PP3M can be summarized as follows. First of all, despite the tolerance demonstrated by patients during the PP1M phase of treatment, adverse events related to paliperidone therapy might appear during PP3M treatment. The control of these side effects, especially if starting soon after a PP3M administration, could be a clinical challenge for psychiatrists but, above all, a real health problem for patients. In addition, a 3-month dosing interval may induce psychiatrists to visit patient less frequently, for example only in concomitance with PP3M administration. Even if pharmacokinetic studies demonstrated a similar exposure to paliperidone with PP3M and PP1M, a 3.5-fold higher dose of PP3M is equivalent to a single dose of PP1M. In other words, a larger quantity of PP is injected in patients treated with PP3M. These data, in addition to the known higher plasmatic mean peak-to-trough ratio of PP3M, could lead to long term adverse effects, somewhat different from those of PP1M.

PP3M injections need more technical carefulness to be correctly administered compared with PP1M procedure. In fact, a longer period of shaking and a longer injecting procedure are required. Lastly, the larger volume administered with PP3M could be more painful in the injected muscle tissue.

### ***Possible study designs to further assess PP3M***

Further studies are needed to assess more clearly PP3M features. Some proposals of study design are described in Figure 3.

**FIGURE 3** Some proposals of study designs needed to assess PP3M features

To our knowledge, the only observational study on PP3M is a retrospective cohort study that chose as index date the date of the first approved claim for PP3M.<sup>76</sup> According to its experimental design, this study does not inform about the effect of PP3M treatment. In this scenery, large pragmatic trials and mirror studies on real-world patients switching from PP1M to PP3M would be useful in defining advantages and disadvantages of PP3M confronted with PP1M. Furthermore, two-arm head-to-head superiority trials could directly compare PP3M with PP1M and with other SGA-LAIs. Regardless of the study design adopted, longer follow-ups are needed to study PP3M treatment safety and impact on patients' adherence, functioning, quality of life, and satisfaction. Finally, further studies are necessary to determine which subgroups of patients would most benefit from PP3M treatment.

## **Conclusions**

In conclusion, PP3M is the only 3-month LAI antipsychotic available on the market. This makes it a unique option of treatment, which can be chosen both in early and advanced phases of illness. Nonetheless, further studies are needed to assess long-term safety, impact on quality of life and on functioning, and to define patients' sub-populations that would most benefit from this new option of treatment

## **Disclosure**

The authors report no conflicts of interest in this work.

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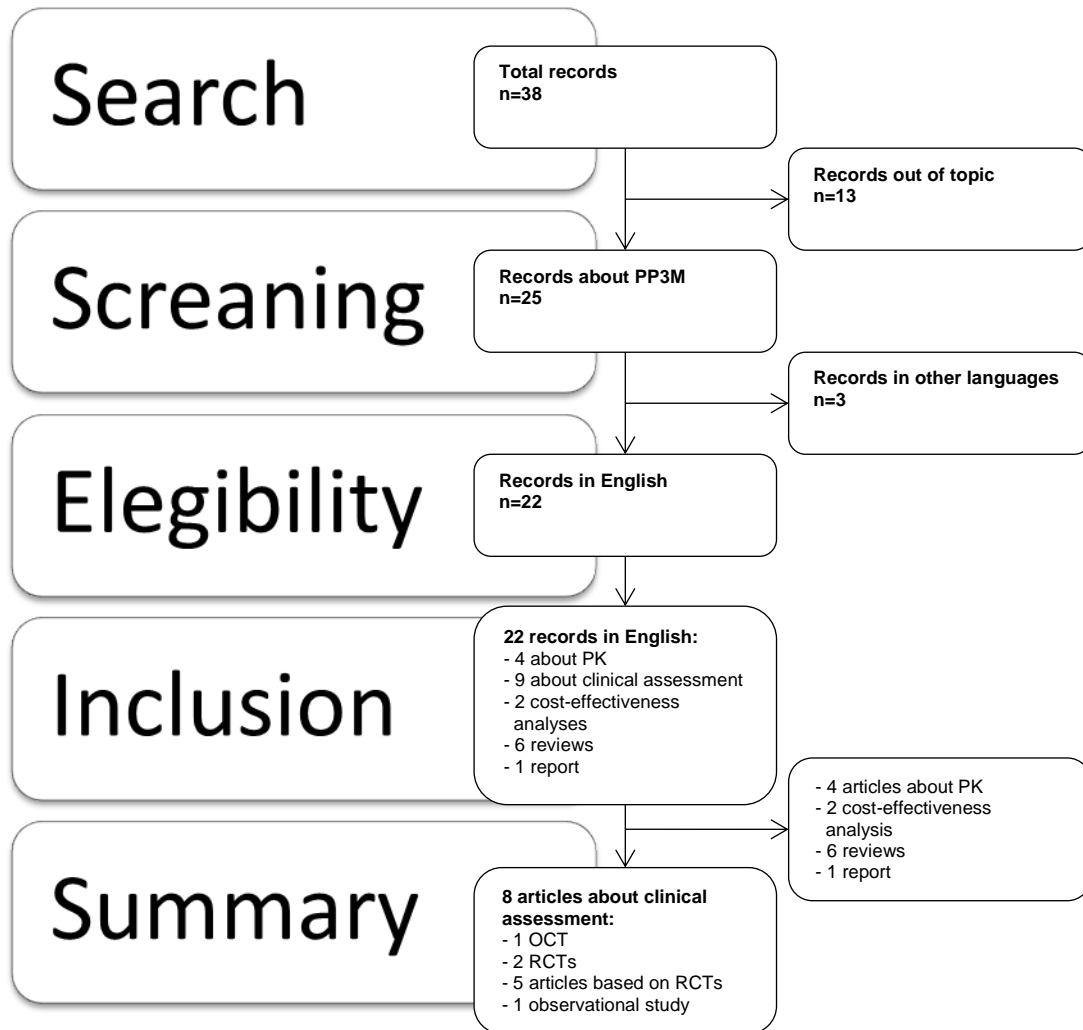
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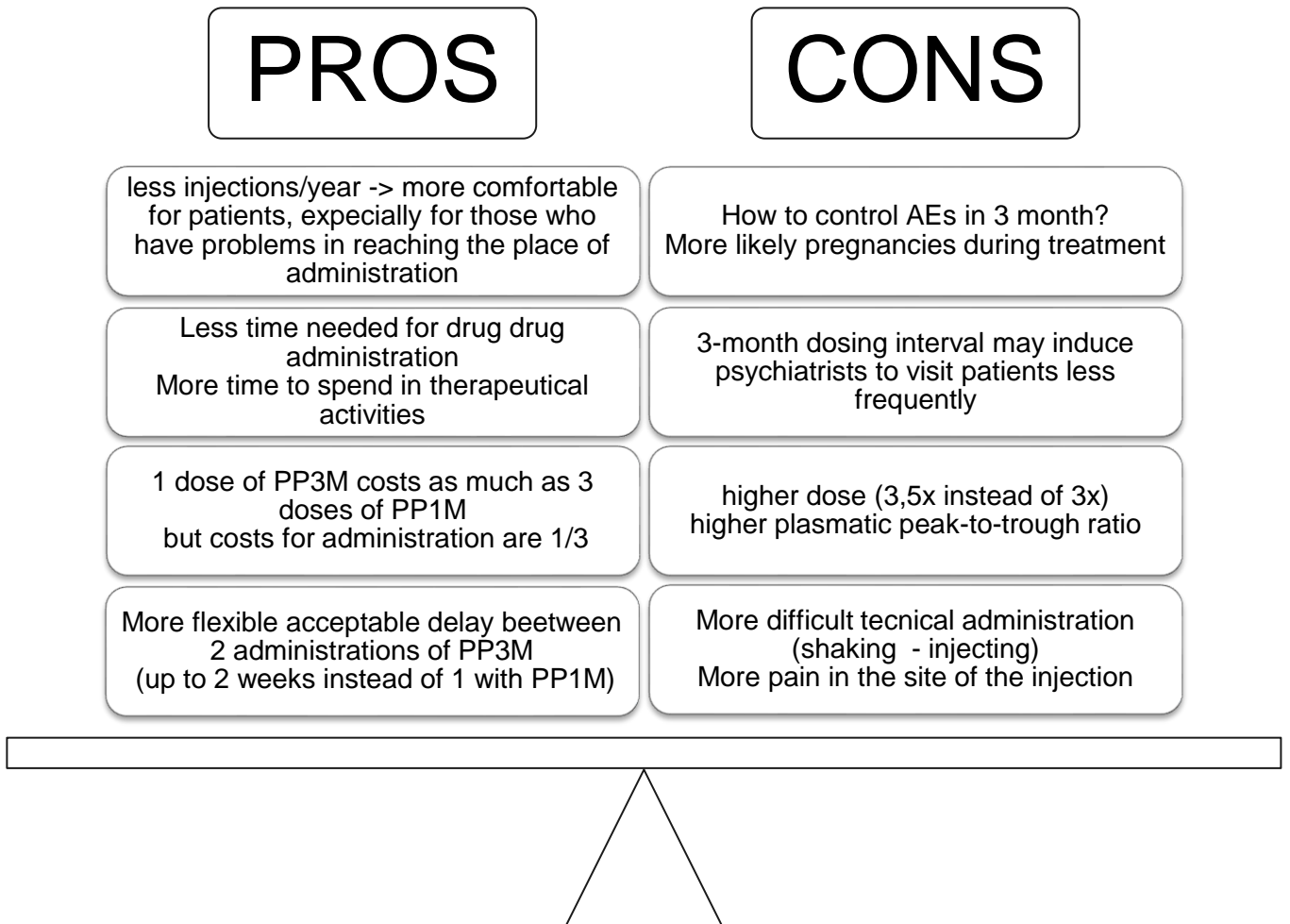
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**Figure 1** Literature search flowchart



OCT: open-label clinical trial; PK: pharmacokinetics; PP3M: paliperidone palmitate 3-month; RCT: randomized clinical trial.

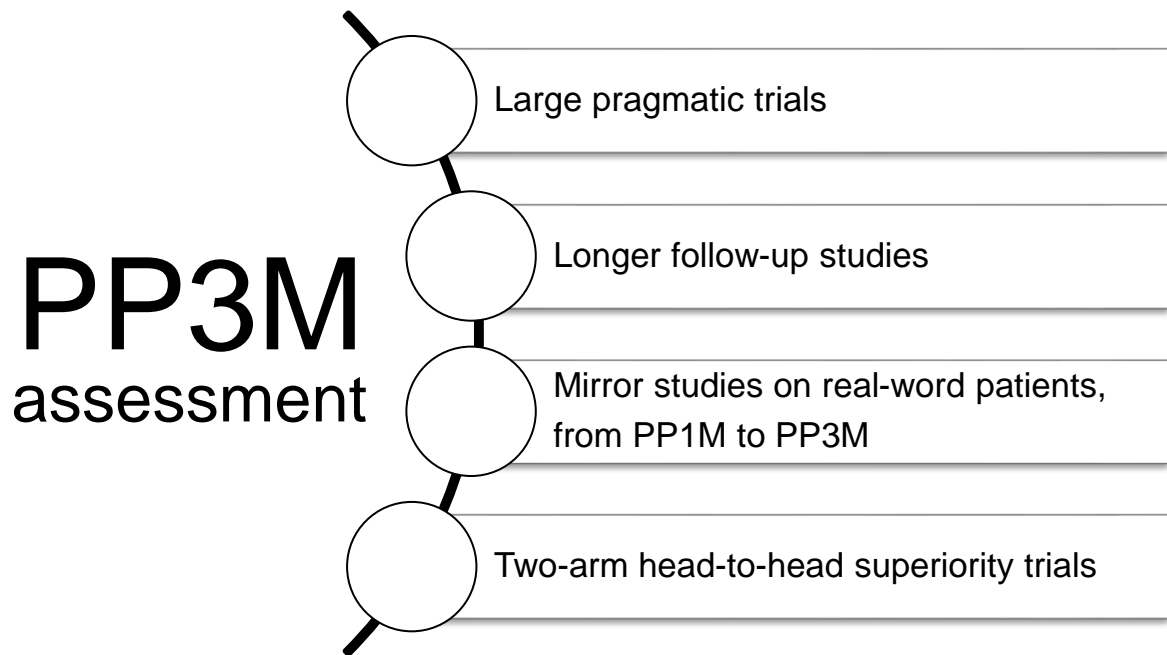
**Figure 2** Comparison between PP3M and PPM1 – Pros & Cons



AE: adverse effect; PP1M: paliperidone palmitate 1-month; PP3M: paliperidone palmitate



**Figure 3** Some possible study designs needed to further assess PP3M



PP1M: paliperidone palmitate 1-month; PP3M: paliperidone palmitate 3-month;