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Corrado Barbui, *Section Editor*

New EMA report on paliperidone 3-month injections: taking clinical and policy decisions without an adequate evidence base

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Three-month long-acting paliperidone is a new, recently marketed, formulation of paliperidone, characterised by the longest available dosing interval among long-acting antipsychotics. The clinical profile of 3-month long-acting paliperidone was recently summarised by the European Medicines Agency (EMA) in a public assessment report, released in April 2016. In this commentary, the main strengths and limitations of the EMA assessment report were appraised and discussed, in order to highlight possible implications for clinical practice, future research and regulatory practices for drug approval.

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In April 2016, the European Medicines Agency (EMA) released a public assessment report on paliperidone palmitate 3-month injections (PP3M), a new long-acting injectable (LAI) formulation of paliperidone that requires an injection once every third month. This new formulation adds to other two already in use formulations: an oral prolonged-release tablet formulation, and a 1-month long-acting formulation (PP1M). The EMA document reported a positive opinion for granting a marketing authorisation for four new strengths of PP3M, with an indication for the maintenance treatment of schizophrenia in adult patients who have been adequately treated with PP1M (European Medicines Agency, Committee for Medicinal Products for Human Use, 2016). The main innovation of PP3M relies in a much slower release in the bloodstream as compared with PP1M. This Commentary critically appraises the clinical data reported in the EMA document, and attempts to identify some of the challenging issues related to the use of PP3M in everyday practice.

The EMA report covers two randomised studies: one phase-3, randomised, double-blind, placebo-controlled trial comparing PP3M *v.* placebo (Berwaerts *et al*. 2015), and one phase-3, randomised, double-blind, head-to-head, non-inferiority trial, comparing PP3M *v.* PP1M (Savitz *et al*. 2016).

The placebo-controlled trial included 305 randomised subjects in the double-blind phase and showed the superiority of PP3M over placebo in terms of relapse prevention (hazard ratio (HR) 3.45; 95%

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confidence interval (CI) 1.73–6.88) (Berwaerts *et al*. 2015). Although comparing a new drug with placebo might be considered ethically debatable and clinically irrelevant when effective agents are available (Barbui & Bighelli, 2013), the 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 (European Medicines Agency, Committee for Medicinal Products for Human Use, 2012). Besides the general validity of these assumptions, it is noteworthy that, in the case of PP3M, previous trials had already shown a beneficial effect of paliperidone *v*. placebo both as oral formulation (relapse rate: relative risk (RR) 0.47, 95% CI 0.34–0.66, seven studies, 1918 patients) and as PP1M (relapse rate: RR 0.58, 95% CI 0.42–0.81, five studies, 2084 patients) (Nussbaum & Stroup, 2012).

In the second, non-inferiority trial, after an open-label phase aimed at achieving clinical stability with PP1M, 1016 patients with schizophrenia were randomised to a fixed dose of PP1M (50, 75, 100 or 150 mg eq./4 weeks) or a fixed dose of PP3M (175, 263, 350 or 525 mg eq./3 months) (Savitz *et al*. 2016). The dose was chosen on the basis of the dose of PP1M at the end of the open-label phase, considering that PP3M requires 3.5-fold higher doses. After 48-weeks of follow-up, at least one relapse occurred in about 8% of patients taking PP3M and 9% of patients taking PP1M, and the differential rate of relapse-free patients was 1.2% (95% CI −2.7 to 5.1). This would demonstrate that PP3M is non-inferior in comparison with PP1M, as the lower limit of the CI does not cross a prespecified 'non-inferiority margin' (Schumi & Wittes, 2011). Such a study design shows some of the prototypical weaknesses of non-inferiority trials. First, as the sample size is calculated on the basis of the sole non-inferiority margin, we cannot establish whether PP3M is better than PP1M (Cipriani *et al*. 2009). Second, a demonstration of non-inferiority leaves uncertainty on whether the two drugs are really equivalent, as there is no validated and shared methodology for reliably choosing the non-inferiority margin, and this is reflected by a lack of clear regulatory advice (Schumi & Wittes, 2011; Wangge *et al*. 2013*b*). Third, exposing patients to studies that do not aim at establishing whether a new drug is associated with additional benefits over a control one may be regarded not only as a waste of resources, but also as a matter of ethical concern (Garattini & Bertele', 2007; Wangge *et al*. 2013*a*). In the case of PP3M, although we may reasonably expect that PP3M and PP1M are similarly effective, we cannot rule out the possibility that a different speed of release into the bloodstream, and a different kinetic profile, may affect acceptability, efficacy and tolerability measures (Ereshefsky & Mascarenas, 2003).

Taken together, the results of these two studies can hardly be used to inform clinical practice, as they were not designed to establish whether PP3M is associated with advantages over PP1M or other LAIs commonly used in clinical practice. Therefore, there is little guidance for case selection (Carpenter & Buchanan, 2015). Remarkably, similar considerations apply to the whole evidence base on LAIs. There are interesting pharmacokinetic features of LAIs that may suggest potential advantages over oral antipsychotics (Ereshefsky & Mascarenas, 2003; Moncrieff, 2006), however systematic reviews of clinical trial data, including a recent meta-analysis of randomised trials comparing oral *v*. LAIs of the same antipsychotic drug, failed to find any differences in terms of efficacy or tolerability (Leucht *et al*. 2011; Kishimoto *et al*. 2014; Misawa *et al*. 2016). Another expected advantage of LAIs would be better treatment adherence. However, randomised trials have never been able to properly assess this pragmatic dimension, as these studies, by definition, have always enrolled participants willing to participate, therefore systematically excluding real-world patients with poor treatment adherence.

As Carpenter and Buchanan wisely pointed out, while decisions should be evidence-based, much of psychopharmacotherapy is conducted without an adequate evidence base (Carpenter & Buchanan, 2015). The choice of a LAI *v*. an oral formulation can be considered a paradigmatic example of this. In the case of PP3M, a longer dosing interval, as compared with other LAIs, may suggest to use this new formulation when adherence in severely ill patients is a major challenge, and also when treating patients who feel uncomfortable with a daily management of oral drugs, and make an informed choice of an injection every 3 months. Doctors and patients should however bear in mind that these considerations are based on common sense only, implying that we do not know if the theoretical beneficial expectations associated with PP3M translate into real advantages in clinical practice, and we do not know about potential unintended consequences. For example, a 3-month dosing interval may induce doctors to visit patients less frequently, and this may in turn negatively affect the doctor–patient relationship, the early recognition of a worsening in symptomatology, and the regular monitoring of safety parameters. Paradoxically, therefore, a longer dosing interval intended to increase patient adherence might actually lower adherence to treatment as a whole, especially in the long-term. Moreover, as the cumulative monthly dose of PP3M is slightly higher than that of PP1M, it

is possible that in the long-term this increased amount of antipsychotic may be associated with consequences in terms of toxicity and tolerability.

Considering the high risk of selection bias and low external validity of existing randomised trials on LAIs, large pragmatic trials would be particularly needed in this field of medicine (Ostuzzi & Barbui, 2016). These trials should ideally enrol unselected samples of everyday patients, aiming to establish the added value of LAIs over standard treatments using pragmatic hard outcome measures. Information on patient perspectives and attitudes towards these formulations is also urgently needed, as it may help clinicians identify when and for which particular group of patients the choice of a LAI should be reasonably considered.

Pragmatic randomised trials may also have a role in informing the drug approval process. We argue that regulatory agencies should require at least one two-arm head-to-head superiority trial, as this would allow to grant a marketing authorisation only for new drugs showing superiority (on a pragmatic efficacy or acceptability outcome) over an active comparator already in use.

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Conflict of interest

None.

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