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Letter to the Editor

Clozapine, a controversial gold standard antipsychotic for the 21st century: Switching to paliperidone palmitate 3-monthly improves the metabolic profile and lowers antipsychotic dose equivalents in a treatment-resistant schizophrenia cohort

Clozapine is an antipsychotic developed in 1961, with a controversial history of side effects. Its superior efficacy was shown in 1988 against the reference antipsychotic until then, chlorpromazine (Kane et al., 1988). Since then, its hegemony as gold standard has been unquestionable and also became the treatment of choice for patients with drug resistant schizophrenia. Despite 40–70% of these patients not responding to clozapine, the efficacy and safety profile of new antipsychotics and their long acting-injectable (LAI) formulations have barely been studied against clozapine (Siskind et al., 2017).

In the last few years, new antipsychotics have emerged such as paliperidone-palmitate (PP), available as both LAI formulations, PP-1-monthly (PP-1M) and the newest PP-3-monthly (PP-3M). Recently, PP-3M has been compared to PP-1M showing a similar efficacy, tolerability, and a lower risk and a latency to relapse after PP-3M treatment discontinuation (Mathews et al., 2018). Moreover, Emond et al. (2019) showed that switching PP-1M to PP-3M was associated with an improvement in compliance, drug abuse and diabetes. In this regard, despite paliperidone having shown a similar efficacy to clozapine (Bai et al., 2017) and that PP-3M has been shown to improve clinical outcomes compared to the monthly and oral forms, no study has been done comparing PP-3M versus clozapine. Therefore, the aim of our study was to carry out an exploratory evaluation of: 1) endocrine profile, 2) hepatic enzymes, 3) blood counts and 4) the use of concomitant psychiatric drugs in treatment-resistant schizophrenics switching from clozapine to PP-3M.

A retrospective mirror study, from 2009 to 2019, was designed (Fig. S1). We included 33 treatment-resistant schizophrenics, ≥18, who lived at the Long-stay Unit of the Luis Valenciano Psychiatry Hospital, Murcia, Spain; they were treated with clozapine as their main antipsychotic, for at least 3 years, firstly switched to PP-1M and consequently modified to PP-3M when available in Spain (October 2016) for at least 3 years. No other antipsychotics were administered during the clozapine withdrawal period. There were no exclusion criteria. Demographical, clinical information (Table S1) and the following parameters were recorded just before switching of clozapine and again following a similar period under treatment with PP: 1) Body Mass Index (BMI), blood levels of glucose, cholesterol, triglycerides and the thyroid stimulating hormone (TSH) to assess the metabolic and endocrine profile, 2) GOT, GPT, GGT liver enzymes and 4) the concomitant psychiatric medications (Doc S1), including the use of other antipsychotics, benzodiazepines and biperiden.

Regarding the treatments we primarily compared the Defined Daily Dose (DDD) developed by the World Health Organization. Because DDD is not an accurate tool to define dose equivalents (Nosè et al., 2008), we also used the haloperidol or diazepam equivalents method for antipsychotics and benzodiazepines, respectively (Leucht et al., 2015; Ashton, 2006). All statistical analyses were performed using the paired student *t*-test for repeated measures. Ethics approval was granted by the corresponding Committee of the Murcia Health Service.

As shown in Fig. 1, PP-3M treatment decreased (A) BMI (25.81 ± 0.9158) significantly ($p = 0.0078$) versus the registered under clozapine treatment (27.76 ± 1.001). PP-3M treatment showed significant decreased levels of (B) glucose (77.18 ± 2.268; $p = 0.0066$); (C) cholesterol (135.2 ± 5.643; $p = 0.0170$), (D) triglycerides (80.09 ± 9.209; $p = 0.0013$) and (E) GGT enzyme (28.45 ± 4979; $p = 0.0371$) versus the previous blood levels when on clozapine treatment (glucose = 85.55 ± 3.379; cholesterol = 146.3 ± 5.270; triglycerides = 106.3 ± 10.01; GGT = 21.64 ± 3.062). No significant differences were found regarding blood counts, TSH and cytolysis liver enzymes. Drug mean doses were 298 mg/day for clozapine and 682 mg/3-monthly for PP-3M, in this case higher than recommended. Nevertheless, 72% of patients were treated with PP-3M, as monotherapy antipsychotic treatment versus 15% of patients who only used clozapine (Table S1). Thus, patients received significantly reduced exposure to antipsychotics under the treatment with PP-3M when compared to clozapine when analyzed by both, the DDD method (3.723 ± 0.3604 vs. 4.919 ± 0.6050; $p = 0.029$) and the haloperidol equivalents method (13.92 ± 1.484 vs. 40.92 ± 4.422; $p < 0.0001$) (Fig. 1F and G). Nevertheless, no significant differences were found when biperiden ($p = 0.499$) or benzodiazepines ($p = 0.784$) were compared between groups.

Our results are in line with previous studies that suggest that the discontinuation of clozapine reduces obesity and diabetes (Schneider et al., 2014). It should be noted that our cohort of patients was under a controlled diet; therefore the metabolic effects shown cannot be attributed to possible changes in lifestyle. Here, we did not discontinue clozapine but we switched it to PP-LAIs also achieving an improvement in the metabolic profile.

Some studies reported an increase in liver enzymes due to clozapine (Douros et al., 2014). However, to the best of our knowledge, this is the first study to show an isolated increase of GGT under clozapine treatment. Several studies suggest a relationship between GGT and obesity (Lee et al., 2007), being proposed as a possible biomarker of central obesity (Coku and Shkembi, 2018).

As current study is a retrospective observational study it is difficult to evaluate the treatments effectiveness due to the lack of mental status records. Nevertheless, our Unit of Psychiatry only admits patients with severe schizophrenia that were primarily treated with clozapine because they met criteria of resistance to antipsychotics. Despite schizophrenia being a chronic disease with acute episodes, our patients remained stable psychopathologically under treatment with PP. To

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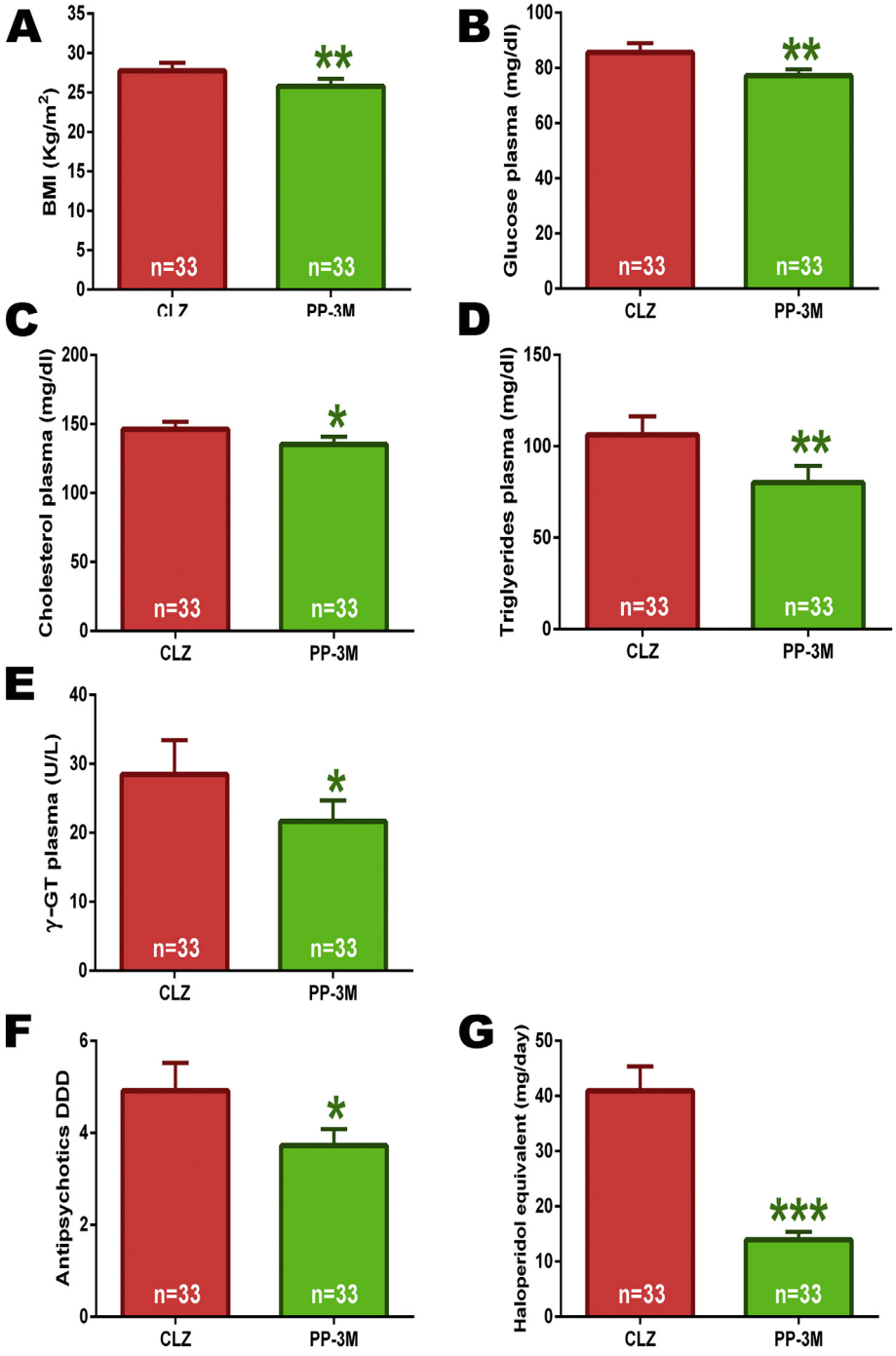

Fig. 1. Endocrine parameters and dosage equivalents under treatment with clozapine (red bars) or paliperidone-3-monthly (green bars). Body Mass Index (A), glucose (B), cholesterol (C), triglycerides (D), GGT enzyme (E), Defined Daily Dose (F) and haloperidol equivalents (G) for antipsychotics. Student *t*-test for repeated measures showed significant differences, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$. Abv: BMI = Body Mass Index; DDD = Defined Daily Dose; CLZ = clozapine; PP-3 M = paliperidone-3-monthly. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

date, only a few studies have been published switching clozapine to other antipsychotics, as aripiprazole or zotepine, showing controversial results (Feeley et al., 2017; Lin et al., 2013). Furthermore, Tiihonen et al. (2017) showed that LAIs treatments are as effective as clozapine in the prevention of acute psychotic episodes in a cohort of >30,000 patients. Here, we showed that switching clozapine to PP not only reduced the metabolic risk but also reduced the dose and number of antipsychotic drugs needed. Furthermore, PP-3M use avoids the periodic tests to control the hematological risk required with clozapine.

We recognize the limitations of our study, mainly the lack of a control group. However, our study allows us to attribute changes in the endocrine profile to the use of clozapine and could be a useful point for future systematic research and to encourage the scientific community to carry out clinical trials comparing PP-3M versus clozapine.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.08.001.

Abbreviations

LAI	long acting-injectable
CLZ	clozapine
PP-1M	paliperidone palmitate 1-monthly

PP-3M	paliperidone palmitate 3-monthly
DDD	Defined Daily Dose
GPT	glutamate-pyruvate transaminase
GOT	glutamic oxaloacetic transaminase
γ-GT	gamma-glutamyl transferase
BMI	Body Mass Index
TSH	thyroid stimulating hormone

Authors' contributions

JAMA contributed to the study design, carried out data collection and contributed to the preparation and editing of the manuscript. JAGC designed the study, carried out statistics, figures and wrote the first and revised drafts of the manuscript. All authors have read and have approved the manuscript.

Declaration of competing interest

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