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Review article

A systematic review of sex-based differences in effectiveness and adverse effects of clozapine

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ABSTRACT

Clozapine is one of the most widely used antipsychotics for treating psychiatric illnesses such as schizophrenia and bipolar disorder. This drug, however, is associated with adverse effects such as weight gain, metabolic syndrome, and blood dyscrasias. The manifestations of mental illness may differ between men and women. Yet, there is little evidence on the influence of sex on treatment response or the occurrence of AEs. To fill this gap of knowledge, we carried out a systematic review of the literature on sex differences in the effectiveness and adverse effects of clozapine. Scant evidence has been published on differences in effectiveness of clozapine between men and women. Indeed, to the best of our knowledge, this issue has only been addressed in a published study. Regarding adverse effects, males have been reported to be more likely to develop metabolic abnormalities such as cholesterol or triglycerides, hypertension, and cardiovascular risk, while females are at a higher risk for gaining weight, developing diabetes, and needing laxatives. Nevertheless, given the scarcity of sex-based studies on this drug, further studies are needed to explore sex-based differences, as the results obtained may be crucial to clinical practice and help improve the quality of life of patients.

1. Introduction

Clozapine was the first atypical antipsychotic to enter clinical use. Nowadays, this drug is widely used for the treatment of a range of psychiatric illnesses associated with psychotic symptoms. Clozapine has been proven to be effective in the management of treatment-resistant schizophrenia and reducing the risk of suicide (Meltzer et al., 2003; Siskind et al., 2017). Clozapine is a 5HT2A/2D antagonist with antipsychotic properties which mechanism of action is based on the inhibition of D2-receptors in the mesolimbic pathway and 5HT2A receptors in the prefrontal cortex, thereby reducing symptoms (Stahl, 2008). This drug also acts on histamine, α-adrenergic and muscarinic receptors, which mediate its antipsychotic and metabolic effects (Nucifora et al., 2017). As a result, clozapine is used with caution, as it has been reported to cause significant adverse effects (AEs) including metabolic abnormalities –such as hypercholesterolemia–, hyperglycemia, and type 2 diabetes (McIntyre et al., 2001; Pérez-Iglesias et al., 2014). In addition, clozapine users are more likely to report constipation as compared to patients on other antipsychotics, being it one of the most frequently reported AEs of this treatment (Shirazi et al., 2016). Clozapine has also been associated with uncommon but serious AEs such as agranulocytosis (Munro et al., 1999), cardiomyopathy, and myocarditis (Michelsen and Meyer, 2007). Moreover, clozapine is the antipsychotic drug that induces the greatest weight gain (Rummel-Kluge et al., 2010). Such side effects may have a negative impact on patient's adherence and quality of life (Lieberman et al., 2005; Parsons et al., 2009).

Differences between sexes have been observed in mental illness manifestations, more specifically, in the severity of symptoms and level of functioning over the course of the illness (Boyd et al., 2015; Ceskova et al., 2015; Ochoa et al., 2012; Talonen et al., 2017; Thorup et al., 2007). In addition, male and female patients respond differently to

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treatment. A variety of studies have revealed that women treated with clozapine are less likely to respond to treatment (Lieberman et al., 1994a,b; Szymansky et al., 1996), although only a few studies have delved into this subject. Women are also more likely to experience metabolic AEs including body mass index (BMI) and blood glucose increase secondary to higher plasma drug concentrations (Anderson et al., 2015; Couchman et al., 2013). Due to the clinical implications of differential sex-based response to treatment, the purpose of this systematic review was to analyze and summarize the latest scientific evidence on differences in response to and adverse effects of clozapine between men and women.

2. Methods

A systematic review was performed based searches on Medline (PubMed), Embase, Cochrane Library and PsycINFO to identify cohort studies, clinical trials, case-control studies, eight or more case series, and systematic reviews published on clozapine in English or Spanish in the last 10 years (2009–2019). MESH and free-text terms in titles and abstracts were used to identify relevant publications. Search was restricted to studies in humans older than 13 years. Search was not restricted to a particular diagnosis. See Table S1 for an example search string. Subsequently, we performed a backward search and manual search of the publications selected.

We included studies which objective was to assess sex differences in response to and/or adverse effects of clozapine. We excluded all studies that did not provide separate results for men and women, did not analyze response to or adverse effects of clozapine or were methodologically flawed.

The quality of the studies selected was assessed separately by two reviewers using the online critical appraisal tools of the Basque Office for Health Technology Assessment (López de Argumedo et al., 2017). These tools help researchers assess the methodological quality of studies by reading articles in detail and analyzing key points. Any disagreements between the reviewers in relation to the inclusion, exclusion or methodological quality of a study were solved by discussion. Only medium or high quality papers were included in this review.

3. Results

Fig. 1 contains a flow chart showing the study selection process in accordance with the PRISMA statement (Moher et al., 2010). A total of 269 publications were retrieved in the initial search, and five more articles were identified using other sources. After titles and abstracts were screened, 232 studies were excluded and 42 were included for full-text review. Finally 11 papers were eligible for inclusion. Overall, we analyzed data on a total of 5890 men and 3086 women treated with clozapine. The characteristics of the studies included are summarized in Table 1.

Of the 11 papers selected for the review, only one analyzed the clinical effects of clozapine (Nielsen et al., 2012). The other 10 articles reported sex differences in clozapine-related adverse effects. The most frequently reported AEs were: metabolic abnormalities, blood dyscrasias (neutropenia, leukopenia or agranulocytosis), cardiovascular risk, weight gain and constipation. Except for a manuscript where diagnosis was not specified, nine studies involved patients with schizophrenia whereas one involved patients with schizophrenia, schizoaffective disorder, bipolar disorder, personality disorder or others.

3.1. Clinical effects

The only study in this review where response to clozapine was assessed was conducted by Nielsen et al. (2012). The authors sought to identify factors associated with better response in schizophrenic patients treated with clozapine. Female sex was associated with more frequent admissions during follow-up (175/47.6% men vs 173/65.8% women, $p = 0.001$) and shorter time to discontinuation ($HR = 1.30$, $p = 0.002$, *95% CI*: 1.10–1.54). Response was poorer in female patients ($OR = 1.84$, $p = 0.001$, *95% CI*: 1.31–2.58); specifically, the rate of response for women was 34.2% vs 52.5% for men ($p < 0.001$). The mean age of patients in this study was 26.2 (*95% CI*: 27.2–28.5) years. Data were retrieved from two databases and a mirror-image design was used to compare pre-clozapine and clozapine periods. The clozapine period extended from the first outpatient prescription of clozapine to clozapine discontinuation or a maximum of two years of treatment.

3.2. Metabolic dysfunctions and homocysteine

We found four studies assessing metabolic dysfunctions associated with clozapine use (Anderson et al., 2015; Bai et al., 2011; Hyde et al., 2015; Ingimarsson et al., 2017). Hypertension was more frequent in men than in women, and men showed a poorer lipid profile. Diabetes or hyperglycemia were more frequent in women. Homocysteine levels in patients with clozapine were only measured in a study, which revealed higher homocysteine levels in men (Wysokinski and Kloszewska, 2013).

Bai et al. (2011) identified factors associated with metabolic symptoms in schizophrenic patients receiving clozapine treatment. For this purpose, the authors performed a retrospective study combined with a cross-sectional survey of 189 hospitalized patients who had been treated with clozapine for at least three months at the time the survey was carried out. Of the total sample, 120 (63.5%) were men and 69 (37.5%) were women, with a mean age of 38.1 (8.54) years. The mean dose of clozapine was 330.3 (106) mg/day. There were no significant differences between men and women either in the risk of developing diabetes mellitus or metabolic syndrome. Nevertheless, male sex was a significant risk factor for high blood pressure, being two times more frequent in men than in women ($OR = 2.046$, $p < 0.01$). The main limitation of this study is that metabolic data prior to clozapine therapy are not provided. The authors indicate the need for further prospective studies where data are collected at different time points.

Hyde et al. (2015) conducted an observational study evaluating 355 patients (243/68.45% males and 111/31.27% females) who were prescribed with clozapine between 2008 and 2012. Patients had diagnoses of schizophrenia, schizoaffective disorder, bipolar disorder, personality disorder or others. Authors found that males were more likely to have impaired high density lipoprotein (HDL) cholesterol ($OR = 3.69$, 95%CI: 1.67–8.16), triglycerides ($OR = 3.31$, 95%CI: 1.13–7.48) and blood pressure ($OR = 5.34$, 95%CI: 1.45–19.68) compared to females. The mean age at which patients started on clozapine was 32.83 years.

Anderson et al. (2015) performed a retrospective survey to analyze dysmetabolic effects related to clozapine treatment in a sample of 100 patients (59 males vs 41 females) with schizophrenia or schizoaffective disorder. Male patients had a mean age of 36.9 years vs 39 years of women. The prescribed mean dose (95% CI) of drug was 433 (389–477) mg/day for males and 425 (388–462) mg/day for females. A significant higher percentage of males had a fasting blood glucose ≤ 6.0 mmol/L (88% vs 41%, $X^2 = 18.6$, $p < 0.0001$), which is defined as normal glucose handling (World Health Organization, 2006). Besides, significantly lower levels of HDL cholesterol were reported for males (mean = 1.1, 95%CI: 0.97–1.4 mmol/L for males vs mean = 1.2, 95%CI: 1.1–1.3 for females; $F = 4.3$, $p = 0.04$). Nevertheless, women had higher plasma clozapine concentrations as compared to men (0.49 vs 0.44 respectively, $F = 2.2$, $p = 0.035$), although no sex differences were observed in plasma norclozapine. Higher clozapine plasma concentrations might increase the risk for weight gain and metabolic dysfunctions in female patients.

Ingimarsson et al. (2017) published a study to analyze the prevalence of type 2 diabetes (T2D) in a sample of Icelandic schizophrenic clozapine-naïve patients. T2D was defined as having a formal diagnosis of T2D, HbA1C≥ 65% in two non-consecutive measurements or two measurements of fasting plasma glucose exceeding 12.6 mg/l. A total of 188 patients were included for analysis, of whom 132 (70.2%) were

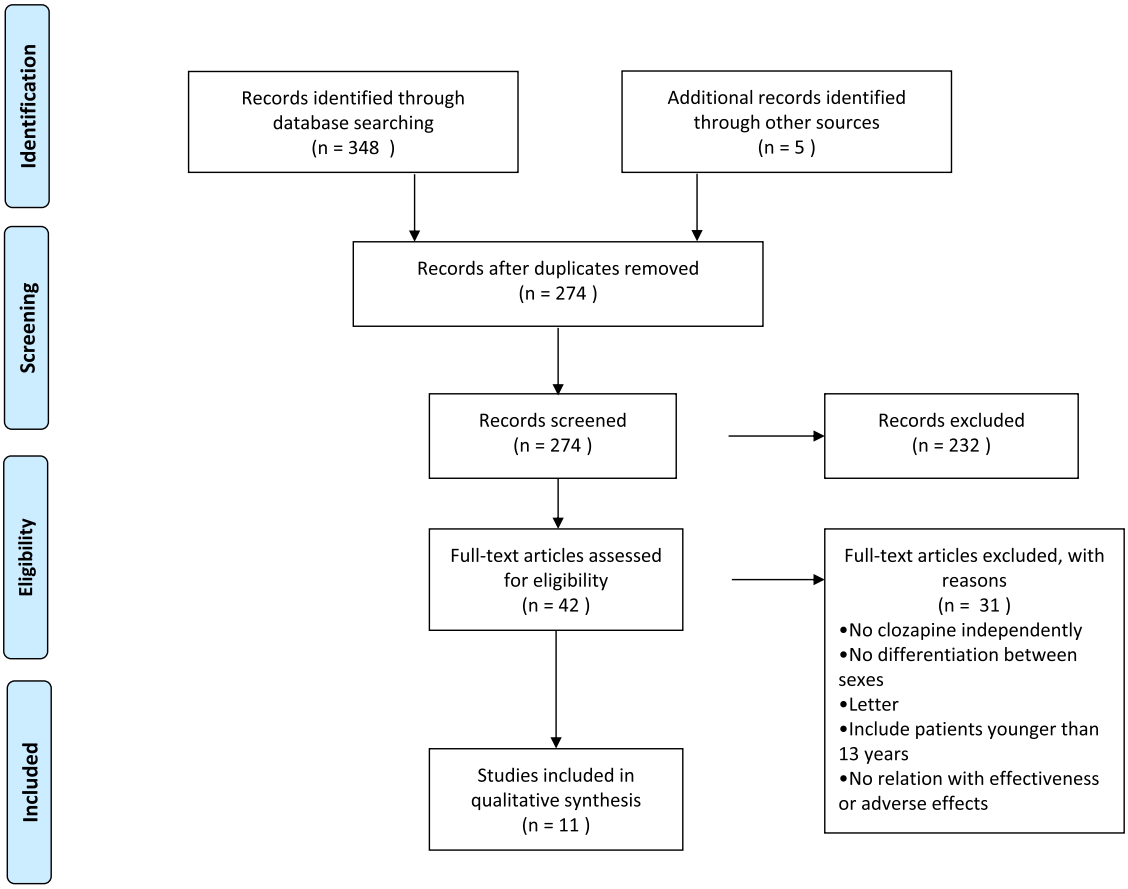

Fig. 1. Prisma flow chart.

male and 56 (29.8%) were female, with a mean age of 51.2 years. Of the total sample, 14.4% of patients had T2D, with a highest prevalence among women (16.1%). This difference, however, was numerically but not statistically significant ($p = 0.32$). Regarding the risk of developing T2D, women and men receiving clozapine were 4.4 and 2.3 times more likely to develop T2D than controls, with significant differences ($p < 0.001$). Of the 27 patients with T2D, 11 (40.7%) males and 5 (18.5%) females were diagnosed with T2D while on clozapine therapy. The authors concluded that establishing the causality of the association between clozapine and T2D is challenging. Yet, the authors urge prescribers to be aware of the risk for developing T2D secondary to the use of clozapine, especially in women.

Wysokinski and Kloszewska (2013) measured levels of blood homocysteine, analyzed body composition, and performed biochemical and anthropometric measurements in a sample of 24 patients with schizophrenia (12/50% males and 12/50% females) on monotherapy with clozapine. Homocysteine levels (17.0 (3.4) vs 12.1 (4.0), $p = 0.009$) and body mass –which were both higher in men– were found to be positively related. These findings led the authors suggest that the usually higher body mass of men might explain that they exhibit higher homocysteine levels. Patients were 38.8 (12.6) years old and took a mean dose of clozapine of 341.1 (148.6) mg/day.

3.3. Blood dyscrasias

Sex-based differences in the incidence of clozapine-induced blood dyscrasias were assessed in three studies (Demler et al., 2016; Hollingworth et al., 2018; Tunsirimas et al., 2019). Although contradictory results were obtained, it seems that leukopenia –but not agranulocytosis– is more frequent in women than in men using clozapine.

In the study published by Demler et al. (2016), the authors examined the role of sex in clozapine-related blood dyscrasias. The authors defined dyscrasia as a white blood cell (WBC) count of less than 3500/mm^3 or an absolute neurotrophil count (ANC) of less than 2000/mm^3 over a three-year follow-up. A total of 193 patients receiving clozapine therapy were included in the study (118/61.1% men, 75/38.9% women; 40–69 years of age). The overall rate of events was higher in men, with an average of 6.4 events per man and 5.2 events per woman. In total, 13 moderate events of leukopenia/granulocytopenia (L/G) were reported, 8 of which were reported in men (61.5%). In contrast, 16% of women (12) did not exhibit any blood dyscrasia event versus 10.2% of men (12). The authors concluded that, surprisingly, women are less likely to have blood dyscrasias and less likely to have this type of events, although they also recommend further research in this field.

Hollingworth et al. (2018) conducted a descriptive study to determine hematological and cardiac clozapine-induced AEs in Australia. Specifically, they focused on neutropenia (including agranulocytosis), myocarditis and cardiomiophaty. Neutropenia is defined as an absolute neutrophil count <1500/microL. The total sample was composed of 6335 patients (4215/66.5% males vs 2120/33.5% females) whose data was obtained from the Australia Therapeutic Goods Administration, which collects AEs reported for all medications. Females were more likely to have neutropenia (OR = 1.45, 95%CI: 1.28–1.67). The mean age of the patients is not reported.

Tunsirimas et al. (2019) performed a retrospective study to investigate the incidence of leukopenia and agranulocytosis among Thai patients with schizophrenia treated with clozapine. They defined leukopenia as total white blood cell <3500 cells/mm^3 and agranulocytosis as neutrophils <500 cells/mm^3. The sample was composed of 641 patients with a mean age of 44.56 (12.06) years, being 413 (64.4%) of them males and 228 (35.6%) females. Authors did not find any case of

Table 1
Description of the studies included in the systematic revision.

Study	Patients		Response to treatment			Adverse effects		Quality of the study
	n	Dx	Dose	Response criteria	Result	Females	Males	
Cohort studies								
Bai et al. (2011)	189 (120/63.5% males, 69/37.5% females)	Schz	Mean 330.3 (106) mg/day	Not assessed			Higher risk of having high blood pressure (≥130/85 mm Hg)	High
Nielsen et al. (2012)	633 (370/58.5% males, 263/41.5% females)	Schz	>100 mg/day	No psychiatric hospitalizations during a 2-year period as an outpatient on clozapine	Higher rates of response in men at 2 years	N/R	N/R	High
Wysokinski and Kloszewska (2013)	24 (12/50% males, 12/50% females)	Schz	Mean 341.1 (148.6) mg/day	Not assessed			Higher lean body mass, homocysteine levels and basal metabolic rate	High
Anderson et al. (2015)	100 (59,759% males, 41/41% females)	TR Schz and schzaff	Males: 433 (389–477) mg/day; females: 425 (388–462) mg/day for females	Not assessed		More likely to have fasting blood glucose ≤6 mmol/L		High
Bailey et al. (2015)	202 (141/69.8% males/61/30.2% females)	Any diagnose	Mean 393.8 mg/day	Not assessed		More likely to be treated with laxatives		Medium
Hyde et al. (2015)	355 (243/68.45% males, 111/31.27% females)	Any diagnose	N/R			More likely to have a BMI ≥ 30	QTc prolongation, impaired HDL, triglycerides and blood pressure	High
Demler et al. (2016)	193 (118/61.1% males, 75/38.9% females)	Schz	N/R	Not assessed			More likely to have blood dyscrasias	Medium
Lau et al. (2016)	117 (67/57% males, 50/43% females)	TR Schz	Initially : 12.5 mg 3 month : 300 mg 12 month : 316 mg	Not assessed		More weight gain. Smokers and those with normal BMI at baseline had greater% wt change.		High
Ingimarsson et al. (2017)	188 (132/70.2% males, 56/29.8% females)	Schz	N/R	Not assessed		More prevalence of T2D		High
Hollingworth et al. (2018)	6335 (4215/66.5% males, 2120/33.5% females)	Schz	N/R	Not assessed		Neutropenia	Myocarditis and cardiomyopathy	Medium
Tunsirimas et al. (2019)	641 (413/64.4% males, 228/35.6% females)	Schz	150 mg/day	Not assessed		Leukopenia		Medium

N/R: Not reported; Schz: schizophrenia; Schzaff: schizoaffective disorder; TR: treatment- resistant; BMI: body mass index; % wt change: percentage of the starting weight; T2D: Type 2 diabetes.

agranulocytosis in this study, but the incidence of leukopenia was 3.1% (20 patients), which was more frequent in females (*OR* = 0.36, $p = 0.026$, 95%CI: 0.14–0.88).

3.4. Cardiovascular risk

Two studies explored clozapine-induced cardiovascular risk (Hollingworth et al., 2018; Hyde et al., 2015).

In the study carried out by Hollingworth et al. (2018), the authors found that both myocarditis and cardiomyopathy were more frequent in males (OR = 1.58, 95%CI: 1.34–1.87 and OR = 2.53, 95%CI: 1.90–3.37, respectively).

Hyde et al. (2015) observed that male schizophrenic patients on clozapine treatment were 6 times more likely to have QTc prolongation as compared to women (OR = 6.17, 95%CI: 2.25–16.88), which is a cardiovascular risk marker.

3.5. Body mass alterations

Two studies on body mass alterations were identified (Hyde et al., 2015; Lau et al., 2016).

In the observational study by Hyde et al. (2015), the authors found that males were half as likely to have a BMI ≥30 during the exposure period (OR = 0.45, 95%CI: 0.24–0.85) as compared to females.

Lau et al. (2016) performed a study to investigate predictors of weight gain and identify the population at greatest risk. The authors explored weight variations from 3 months to 12 months, expressing results as a percentage of baseline body mass at 3 months (%wtchange). They analyzed 117 patients (67/57% males, 50/43% females) with treatment-resistant schizophrenia. Patients had a mean age of 34.5 (10.7) years. The starting dose of clozapine was 12.5 mg/day, which was up-titrated up to 316 mg at 12 months. In this study, females were significantly more likely to gain weight than men ($p = 0.001$). Further, BMI at 3 months and smoking status were independent predictors of the %weight change at 3 months in females ($p = 0.02$ and $p = 0.002$ respectively), but not in males ($p = 0.882$ and $p > 0.1$ respectively).

3.6. Constipation

In the study of Bailey et al. (2015), the authors seeked to identify predictive factors of clozapine-induced constipation. Bailey et al. (2015) found that women were more likely to use laxatives than male (OR = 0.42, $p < 0.001$, 95%CI: 0.23–0.79). The sample was composed of 202 outpatients treated with clozapine for a minimum of three months, of whom 141 (69.8%) were men and 61 (30.2%) were women, with a mean age of 44.6 years. The average clozapine dose was 393.8 mg/day. As male sex is generally associated with a higher use of laxatives, the authors suggest that men may be less likely to report constipation than women. Besides, the authors identify it as a limitation that some patients may have constipation unrelated to the use of clozapine and that adherence or the efficacy of the laxative therapies is not guaranteed.

4. Discussion

The results of this systematic review on sex differences in response to clozapine reveal a clear lack of solid evidence, as they were only explored in one study (Nielsen et al., 2012). According to this result, women were less likely to respond to treatment (*OR* = 1.84). Otherwise said, hospital admissions at 2 years of treatment were more likely in women. These results are consistent with the results previously reported by other authors (Lieberman et al., 1994a,b; Umbricht et al., 2002). However, opposite results have been obtained by other researchers, who report better response in women as compared to men (Usall et al., 2007). Therefore, although in general female sex is associated with better response to antipsychotics in schizophrenia, in the case of clozapine this relation is not yet clear.

In terms of adverse effects, the most solid evidence published is related to metabolic disturbances. Our results suggest that men have an increased risk for developing metabolic abnormalities. Specifically, events related to blood pressure, triglycerides and HDL cholesterol were more frequent in men (Anderson et al., 2015; Bai et al., 2011; Hyde et al., 2015). This is in line with the results obtained in previous studies where clozapine was associated with hypertriglyceridemia and reduced HDL (Bodén et al., 2013; Gaulin et al., 1999; Leitão-Azevedo et al., 2006). Besides, men were also more likely to exhibit higher homocysteine levels than women (Wysokinski and Kloszewska et al., 2013). High values of this blood aminoacid may induce cardiovascular diseases. In fact, another relevant result of this review is that men tend to be more likely to have QTc prolongation, myocarditis and cardiomyopathy (Hyde et al., 2015; Hollingworth et al., 2018). Nevertheless, no sex differences were found in previous studies in relation to antipsychotic-induced QTc prolongation. In some studies women were found to be more likely to experience this event (Grande et al., 2011; Lin et al., 2004; Yang et al., 2011). Therefore, although our results suggest a higher risk for developing antipsychotic-induced QTc prolongation for males, this association remains unclear. Alternatively, in this review we observed that women on clozapine were at a higher risk of developing diabetes (Anderson et al., 2015; Ingimarsson et al., 2017). Specifically, in the study of Anderson et al. (2015), females exhibited higher levels of glycemia and exceeded normal values more frequently than males (≤6 mmol/L), which is a biomarker of diabetes. These authors also document higher clozapine plasma concentrations in women than in men using the same dose. As a result, clozapine therapy may be a risk factor for weight gain. These results support those reported both, by Hyde et al. (2015), who documented that males were half as likely to have a BMI ≥ 30 during the study period; and by Lau et al. (2016), who reported higher weight gain in females as compared to males taking clozapine. Other authors have also observed higher weight gain related to the use of clozapine in women (Aichhorn et al., 2006; Kraal et al., 2017). This phenomenon might be explained by estrogen-induced CYP1A2 inhibition, the primary enzyme involved in the metabolism of clozapine. This may also explain the slower clearance and better treatment adherence observed in women (Bigos et al., 2008; Díaz et al., 2004; Sellwood and Tarrier, 1994).

Regarding blood dyscrasias, Demler et al. (2016) found that their prevalence was higher in men, which is in agreement with the results obtained by Maher et al. (2013) in children. These authors reported that male sex was a significant risk factor for moderate neutropenia (absolute neutrophil count values $<1500/mm^3$). In contrast, Hollingworth et al. (2018) and Tunsirimas et al. (2019) reported that women were more likely to experience neutropenia and leukopenia (total white blood cell count <3500 cells/mm^3). This pattern has also been observed in previous studies (Alvir et al., 1993; Balda et al., 2015).

Finally, although we found in the scientific literature several works reporting no sex differences in gastrointestinal hypomotility (Chougule et al., 2018; Shirazi et al., 2016), in our review females were more likely to use laxatives (Bailey et al., 2015). This result suggests that males are at a higher risk of complications as they are more reluctant to report constipation. In any case, clinicians should be careful and ask patients regularly in order to prevent serious complications secondary to untreated clozapine-induced constipation.

A limitation of this study is that the majority of the manuscripts involved schizophrenic patients. However, there is no evidence that these results could be applied to bipolar patients. Therefore, the results of this review cannot be generalized to other psychiatric disorders. Another limitation is that clozapine is generally prescribed to treatment-resistant patients who have previously taken or are currently taking concomitant medication. This implies that the results obtained could not only be attributable to clozapine but also to the influence of previous treatments.

In conclusion, there is very limited evidence on sex-based

differences in the effectiveness of clozapine, as we only found a study assessing this aspect. Regarding adverse effects, our results suggest that males taking clozapine are at a higher risk for developing metabolic abnormalities and cardiovascular diseases. This is relevant to clinical practice, given that a higher proportion of male patients are prescribed with clozapine. Females were more likely to experience weight gain, develop diabetes and use laxatives. Although there are other antipsychotics such as amisulpride, aripiprazole and ziprasidone that cause a more moderate weight gain (Bai et al., 2017; Bak et al., 2014; Tek et al., 2016), these have been shown to be less effective in clinical terms than clozapine (Ifteni et al., 2014; McEvoy et al., 2006; Stroup et al., 2016).

Further studies are needed to better understand sex-based differences in the occurrence of AEs associated with the use of clozapine. The results obtained from these studies would be of clinical relevance, as they would help improve the quality of life of patients. Thus, if the occurrence of AEs could be predicted, measures could be adopted to prevent treatment discontinuance.

Declaration of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.112506.

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