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The effects of second-generation antipsychotics in borderline personality disorder – a systematic review.

Os efeitos dos antipsicóticos de segunda geração na perturbação de personalidade borderline – uma revisão sistemática.

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Doutora Adelaide Susana Ferreira da Costa

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UC Dissertação/Projeto (6º Ano) - DECLARAÇÃO DE INTEGRIDADE

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DESIGNAÇÃO DA ÁREA DO PROJECTO

3.2.- Medicina Clínica (Psiquiatria)

TÍTULO DISSERTAÇÃO/~~MONOGRAFIA~~ (riscar o que não interessa)

The effects of second-generation antipsychotics in borderline personality disorder - a systematic review

ORIENTADOR

Adelaide Susana Ferreira da Costa

COORIENTADOR (se aplicável)

ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
É AUTORIZADA A REPRODUÇÃO PARCIAL DESTE TRABALHO (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
DE ACORDO COM A LEGISLAÇÃO EM VIGOR, (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) NÃO É PERMITIDA A REPRODUÇÃO DE QUALQUER PARTE DESTE TRABALHO.	☒

Faculdade de Medicina da Universidade do Porto, 09/07/2021

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Dedicatória

Dedico este trabalho a todas as pessoas que me acompanharam neste percurso árduo e desafiante. Em primeiro lugar, à minha família pelo apoio e todo o investimento que tiveram em mim durante toda a vida. Em segundo lugar, aos meus amigos e colegas de curso pelo companheirismo e partilha de experiências durante o mesmo. Em último, mas não menos importante, à Professora Doutora Adelaide Costa por ter aceite orientar o meu projeto e pela paciência e compreensão demonstrada até à conclusão da tese.

Todas estas pessoas têm a mais profunda gratidão da minha parte por presenciarem e auxiliarem na concretização desta etapa tão importante!

Baltazar Oliveira

The effects of second-generation antipsychotics in borderline personality disorder – a systematic review.

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Abstract

Borderline personality disorder (BPD) is a convoluted psychiatric disease that requires a considerable amount of health resources to be adequately treated. Previous studies have shown that pharmacotherapy can be advantageous for BPD. Within the drugs tested, second-generation antipsychotics (SGAs) showed an improvement in BPD-specific outcomes in these patients when compared to placebo. However, the amount of evidence available at the time of the last review in this subject was insufficient to justify its recommendation. The aim of this systematic review is to qualitatively assess randomized controlled trials (RCTs) of SGAs in BPD patients currently available through search. Database searches were performed using MEDLINE, SCOPUS, ISI Web of Knowledge and PsycInfo. Study selection and data collection were carried out independently by two researchers. Out of 1294 records (without duplicates), nine studies were included in this review. The results confirm the findings of a previous review. Most SGAs show a significant decrease in various BPD symptoms in comparison to placebo. Current findings suggest SGAs are effective against BPD and can serve as co-treatment with psychotherapy. Further RCTs are needed with larger samples and with head-to-head comparisons between different drugs.

Keywords: Borderline Personality Disorder, Antipsychotic Agents, Olanzapine, Aripiprazole, Ziprasidone, Quetiapine Fumarate, Systematic Review.

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1. Introduction

According to the DSM-5, Borderline Personality Disorder (BPD) is a Cluster B personality disorder, which core symptoms are: affect instability, impulsiveness, aggressiveness, unstable interpersonal relationships, chronic feelings of emptiness, self-mutilation and recurrent suicidal behaviors. Its prevalence in the american population is estimated to vary between 1.6% and 5.9% (American Psychiatric Association, 2013). BPD is a contentious and complex disorder associated with high levels of impairment for these patients and with high spending of mental health resources (Zanarini et al., 2004). The majority of people with BPD usually have other psychiatric comorbidities like mood disorders, anxiety disorders, substance use disorders and eating disorders (Grant et al., 2008; National Collaborating Centre for Mental Health, 2009).

There has been growing evidence to support the use of psychotherapy in BPD (Oud et al., 2018). There are countless modalities of approved psychotherapies for BPD: Dialectical Behavior Therapy (DBT), mentalization-based treatment, transference-focused therapy and schema therapy (Lieb et al., 2010; National Collaborating Centre for Mental Health, 2009; Oud et al., 2018).

Even though there is not a specific drug recommended specifically for BPD, the high prevalence of comorbidities causes pharmacotherapy to become a part of the management of these patients (American Psychiatric Association, 2013; Lieb et al., 2010; National Collaborating Centre for Mental Health, 2009). Some of the most used drugs are antidepressants, mood stabilizers and antipsychotics. Typical antipsychotics (e.g. haloperidol) have been proven to be effective in some BPD-specific symptoms when compared with placebo (Lieb et al., 2010). However, their adverse effects can be serious and impairing, such as extrapyramidal symptoms. Therefore, there is a need for an alternative to be used instead in clinical practice.

Second-generation antipsychotics (SGAs) or atypical antipsychotics are generally safer to administer than typical antipsychotics (Farah, 2005). Their mechanism of action is variable, but it generally encompasses partial antagonism of the dopamine-2 (D2) receptors and antagonism of serotonin receptors 2A and 2C (Farah, 2005). Even though their use is not specifically recommended for BPD (according to the NICE 2009 guidelines), SGAs are frequently prescribed off-label (Lieb et al., 2010; National Collaborating Centre for Mental Health, 2009).

A previous systematic review of Randomized Controlled Trials (RCTs) made by Lieb et al. (2010) showed that both olanzapine and aripiprazole reduced the core symptoms of BPD when compared with placebo, most notably impulsivity, psychotic symptoms and interpersonal hardships (Lieb et al., 2010). However, the evidence was not robust, and they recommended further research (Lieb et al., 2010). Since more than ten years have passed, new findings may be available for review. It is important to assess the efficacy of SGAs because pharmacotherapy should be targeted for specific symptoms of BPD, and to avoid polypharmacy, there is a need to produce high quality evidence-based decisions in treating these patients (Lieb et al., 2010).

The aim of this systematic review is to update on the state of the art regarding the effects of SGAs in people with BPD through a qualitative assessment of RCTs.

2. Methods

2.1. Inclusion criteria and search query

For this systematic review, RCTs studying atypical antipsychotics in patients with diagnosed BPD were included up to March 3rd, 2021. Inclusion criteria are as follows: being a RCT, having an intervention group consisting of an atypical antipsychotic and having patients with BPD. Studies were excluded if they had no placebo group as comparison. There were no language or data restrictions applied. A search was performed in the following electronic databases: MEDLINE, SCOPUS, ISI Web of Knowledge and PsycInfo. The search query included the keywords “borderline personality disorder”, “Antipsychotic Agents”, “Aripiprazole”, “Olanzapine”, “Quetiapine”, “controlled trial”, “RCT” and “placebo”. In order to obtain an evidence-based search strategy to find clinical trials, two InterTASC filters for RCTs were used in MEDLINE and PsycINFO (Eady et al., 2008; Lefebvre et al., 2021). Table 1 presents the search strategy in more detail. Additionally, some references were retrieved from the last review made by Lieb et. al (2010).

Table 1. Search strategies used in electronic databases.

Electronic Database	Search Date	Search Strategy	Nº of results
MEDLINE[a]	03/03/2021	("borderline personality disorder"[MeSH Terms] OR "borderline"[Title/Abstract] OR "personality disorder"[Title/Abstract] OR "bpd"[Title/Abstract] OR "personality disorders"[Title/Abstract]) AND ("antipsychotic*"[Title/Abstract] OR "atypical antipsychotic*"[Title/Abstract] OR "second generation antipsychotic*"[Title/Abstract] OR "antipsychotic agents"[MeSH Terms] OR "olanzapine"[Title/Abstract] OR "aripiprazole"[Title/Abstract] OR "quetiapine"[Title/Abstract] OR "risperidone"[Title/Abstract]) AND (("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "drug therapy"[MeSH Subheading] OR ("randomly"[Title/Abstract] OR "trial"[Title/Abstract] OR "groups"[Title/Abstract])) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]))	604
SCOPUS	03/03/2021	TITLE-ABS-KEY(borderline personality disorder) OR TITLE-ABS-KEY(personality disorder) OR TITLE-ABS-KEY(personality disorders) OR TITLE-ABS-KEY(BPD) AND TITLE-ABS-KEY(antipsychotic) OR TITLE-ABS-KEY(antipsychotics) OR TITLE-ABS-KEY(olanzapine) OR TITLE-ABS-KEY(aripiprazole) OR TITLE-ABS-KEY(quetiapine) OR TITLE-ABS-KEY(risperidone) AND TITLE-ABS-KEY(randomized controlled trial) OR TITLE-ABS-KEY(randomized) OR TITLE-ABS-KEY(trial) OR TITLE-ABS-KEY(placebo)	820
ISI Web of Knowledge	03/03/2021	(TS=(borderline personality disorder) OR TS=(personality disorder*) OR TS=(BPD)) AND (TS=(antipsychotic*) OR TS=(olanzapine) OR TS=(aripiprazole) OR TS=(quetiapine) OR TS=(risperidone)) AND (TS=(randomized controlled trial) OR TS=(randomized) OR TS=(trial*) OR TS=(placebo))	333
APA PsycInfo[b]	03/03/2021	(TI borderline personality disorder OR AB borderline personality disorder OR TI personality disorder OR AB personality disorder OR TI BPD OR AB BPD) AND (TI Antipsychotic OR AB Antipsychotic OR TI Antipsychotics OR AB antipsychotics OR TI olanzapine OR AB olanzapine OR TI aripiprazole OR AB aripiprazole OR TI quetiapine OR AB quetiapine OR TI risperidone OR AB risperidone) AND (TI placebo OR AB placebo OR TI random OR AB random OR TI exp treatment OR AB exp treatment)	68

[a] Use of MEDLINE InterTASC filter for Randomized Controlled Trials (Lefebvre et al., 2021).
[b] Use of PsycInfo InterTASC filter for Randomized Controlled Trials (Eady et al., 2008).

2.2. Study selection

Studies were first screened through reading of titles and abstracts. After the screening, full-texts of eligible articles were retrieved and read thoroughly before deciding to include or exclude. The authors of the studies were contacted to retrieve some full-texts. This process was performed independently by two reviewers. In case of disagreement, consensus did the resolution.

2.3. Data collection

Data from each study regarding study design, participants, methods, intervention, outcomes and main findings were collected through a spreadsheet form. The outcomes of interest are the various scales used to measure BPD symptomology (e.g. ZAN-BPD scale, CGI-BPD scale, OAS-M scale, …). The main findings of each study consist of statistically significant results ($p < 0.05$) between-groups. Within-group differences were not assessed. This process was performed independently by two reviewers. In case of disagreement, consensus did the resolution.

2.4. Assessing risk of bias

Risk of bias of each study was performed according to the Cochrane Risk of Bias Tool (Higgins et al., 2019) using the software program *RevMan*. This Risk of Bias Tool assesses the following domains: random allocation sequence, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, conflicts of interest and other bias (Higgins et al., 2019). This assessment was only done at the overall study level and did not account for the risk of bias for each specific outcome. This process was only done by the author.

3. Results

3.1. Study selection

The search performed retrieved 1834 records (1294 without duplicates). After that, the selection of studies was carried out as described in Figure 1. In the end, nine RCTs (corresponding to ten articles) met the inclusion criteria and were eligible to be included in this review.

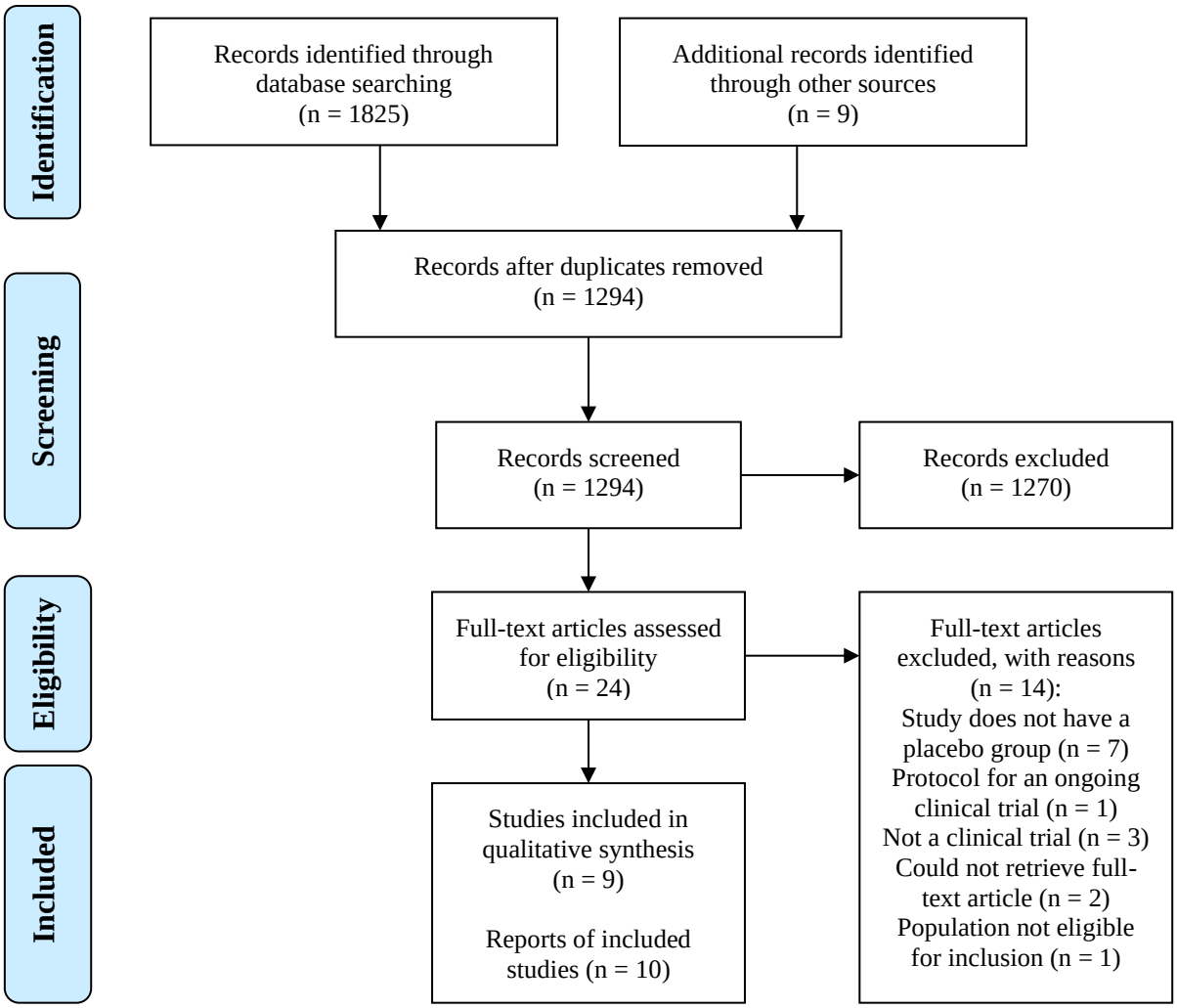

Figure 1. PRISMA Flowchart for study selection (Moher et al., 2009).

3.2. Characteristics of the included studies

The included studies were all double-blinded RCTs in an outpatient setting and used an intention-to-treat analysis (ITT) to assess their outcomes. While the majority of studies used variable doses of antipsychotic, three used fixed doses (Black et al., 2014; Nickel et al., 2006; Zanarini et al., 2011). Two RCTs applied DBT in both groups (Linehan et al., 2008; Soler et al., 2005), while another used nonspecific psychotherapy (Pascual et al., 2008). Most of the included studies used a last observation carried forward (LOFC) analysis for the participants who dropped out (Black et al., 2014; Bogenschutz and George Nurnberg, 2004; Pascual et al., 2008; Schulz et al., 2008; Soler et al., 2005; Zanarini et al., 2011). It should be noted Nickel et al. (2006) reported in a different article the results of their outcomes 18 months after the experiment (Nickel et al., 2007).

Table 2 describes the main characteristics of each study. As it can be observed, most of their inclusion criteria required a diagnosis of BPD according to the DSM-IV criteria (American Psychiatric Association, 2000) and having at least a moderate severity of illness, except in these clinical trials: Zanarini et al. (2001), Bogenschutz et al. (2004) and Nickel et al. (2006). In general, the exclusion criteria applied did not vary much between RCTs. Patients were mostly excluded if they met diagnostic criteria for schizophrenia, schizoaffective disorder, other psychotic disorders or if they were actively suicidal. While two studies allowed patients to have some active comorbidities (e.g. major depression, substance use disorder) (Linehan et al., 2008; Nickel et al., 2006), most them excluded patients if they had an active psychiatric disorder other than BPD. Most comorbidities present (active or inactive) within the participants were depressive disorders, anxiety disorders, substance use disorders and eating disorders (Linehan et al., 2008; Nickel et al., 2006; Schulz et al., 2008; Zanarini et al., 2011). The only significant baseline differences found between the intervention and placebo groups were in Pascual et al. (2008) and Black et al. (2014). The first RCT encountered significant differences in Hamilton Depression Rating (HAM-D) scores between olanzapine and placebo groups at the beginning. However, they addressed this finding adequately by performing Analysis of Covariance (ANCOVA) (Pascual et al., 2008). The latter found baseline differences in Zanarini Rating Scale for BPD (ZAN-BPD), Over Aggression Scale Modified (OAS-M), Symptom-Checklist 90 Revised (SCL-90-R) and Sheehan Disability Scale scores. To account for these differences, a mixed-effects model was used (Black et al., 2014).

Table 2. Characteristics of included studies

Studies	Design	Location	Duration, weeks	Drug used (mean dose)	Nº of participants (drug/placebo)	Population	Mean age (SD), years		Sex, % of Females	Study completion, % of participants	Outcomes
							Drug	Placebo			
Zanarini et al., 2001	Double-blinded RCT	United States	24	Olanzapine (5.33 mg/day)	19/9	Women with BPD	27.6 (7.7)	25.8 (4.5)	100	32.1	SCL-90 (Primary), HAM-D, DES, PANSS, GAF
Bogenschutz et al., 2004	Double-blinded RCT	United States	12	Olanzapine (6.9 mg/day)	16/19	People with BPD	Total: 32.6 (10.3)		62.5	65.7	CGI-BPD (Primary), CGI, HAM-D, HAM-A, OAS-M AIAQ
Soler et. al., 2005	Double-blinded RCT	Spain	12	Olanzapine (8.83 mg/day)	30/30	People with BPD and CGI score ≥4	27.57 (6.3)	26.33 (5.4)	88.3	70	HAM-D, HAM-A, CGI, Behavioral reports for self-injury/suicide attempts, impulsiveness and emergency unit visits
Nickel et al., 2006	Double-blinded RCT	Germany, Austria	8[c]	Aripiprazole (15 mg/day)	26/26	People with BPD	22.1 (3.4)	21.2 (4.6)	82.7	90.4	SCL-90-R (Primary), HAM-D, HAM-A and State-Trait Anger Expression Inventory
Linehan et al., 2008	Double-blinded RCT	United States	21	Olanzapine (4.46 mg/day)	12/12	Women with BPD and OAS-M score ≥6	Total: 36.8 (9.0)		100	67	OAS-M, HAM-D, Therapeutic Monitoring Records
Pascual et al., 2008	Double-blinded RCT	Spain	12	Ziprasidone (84.1 mg/day)	30/30	People with BPD and CGI score ≥4	29.10 (5.96)	29.33 (6.33)	81.7	48.3	CGI-BPD, HAM-D, HAM-A, Barratt Impulsiveness Scale, Buss-Durkee Inventory
Schulz et al., 2008	Double-blinded RCT	Multicenter[a]	12	Olanzapine (7.09 mg/day)	155/159	People with BPD and ZAN-BPD score ≥9	31.8 (9.5)	31.8 (9.6)	71.0	56.7	ZAN-BPD (Primary), SCL-90-R, OAS-M, MADRS, Sheehan Disabilty Scale
Zanarini et al., 2011	Double-blinded RCT	Multicenter[b]	12	Olanzapine (2.5 mg/day, 5-10 mg/day)	150[d]/148[d]/153	People with BPD and ZAN-BPD score ≥9	32.6 (11.2)[d] 32.8 (10.0)[d]	33.5 (11.3)	73.6	65.2	ZAN-BPD (Primary), SCL-90-R, OAS-M, MADRS, Sheehan Disabilty Scale
Black et al., 2014	Double-blinded RCT	United States	8	Quetiapine (150 mg/day, 300 mg/day)	33[e]/33[e]/29	People with BPD and ZAN-BPD score ≥9	28.2 (8.0)[e] 30.2(8.1)[e]	30.1 (8.8)	70.5	67	ZAN-BPD, OAS-M, MADRS, GAF, SCL-90-R, Sheehan Disability Scale, Barratt Impulsiveness Scale

[a] Belgium, France, Germany, Norway, Portugal, Spain, Sweden, United Kingdom and United States.
[b] United States, Italy, Poland, Romania, Turkey, Chile, Peru, Argentina, and Venezuela.
[c] Nickel et al. proceeded to assess the outcomes for 18 months after the experimental phase (Nickel et al., 2007).
[d] Data relative to Olanzapine 2.5 mg/day and 5-10 mg/day, respectively.
[e] Data relative to Quetiapine 150 mg/day and 300 mg/day, respectively.
Abbreviations: RCT=Randomized Controlled Trial, SD=Standard Deviation, BPD=Borderline Personality Disorder, SCL-90=Symptom Checklist-90, SCL-90-R=SCL-90 Revised, GAF=Global Assesment of Functioning Scale, PANSS= Positive and Negative Syndrome Scale, DES=Dissociative Experiences Scale, CGI=Clinical Global Impressions Scale, CGI-BPD=CGI modified for BPD, OAS-M=Overt Agression Scale Modified, AIAQ=Anger, Irritability and Assault Questionnaire, MADRS= Montgomery-Âsberg Depression Rating Scale, ZAN-BPD=Zanarini Rating Scale for BPD.

3.3. Risk of bias in the included studies

The risk of bias in each study was assessed and can be observed in Figure 2. According to the risk of bias graph presented in Figure 3, these studies have in general a low risk of bias due to blinding and selective reporting when it comes to outcomes reported in the study. However, eight out of nine studies had a high risk of conflict of interest (most researchers received grants or research support from pharmaceutical companies), which may have an influence on their findings. Furthermore, numerous studies provided insufficient data regarding allocation concealment. Moderate to high dropout rates in these trials are to be expected, so there is higher risk for attrition bias.

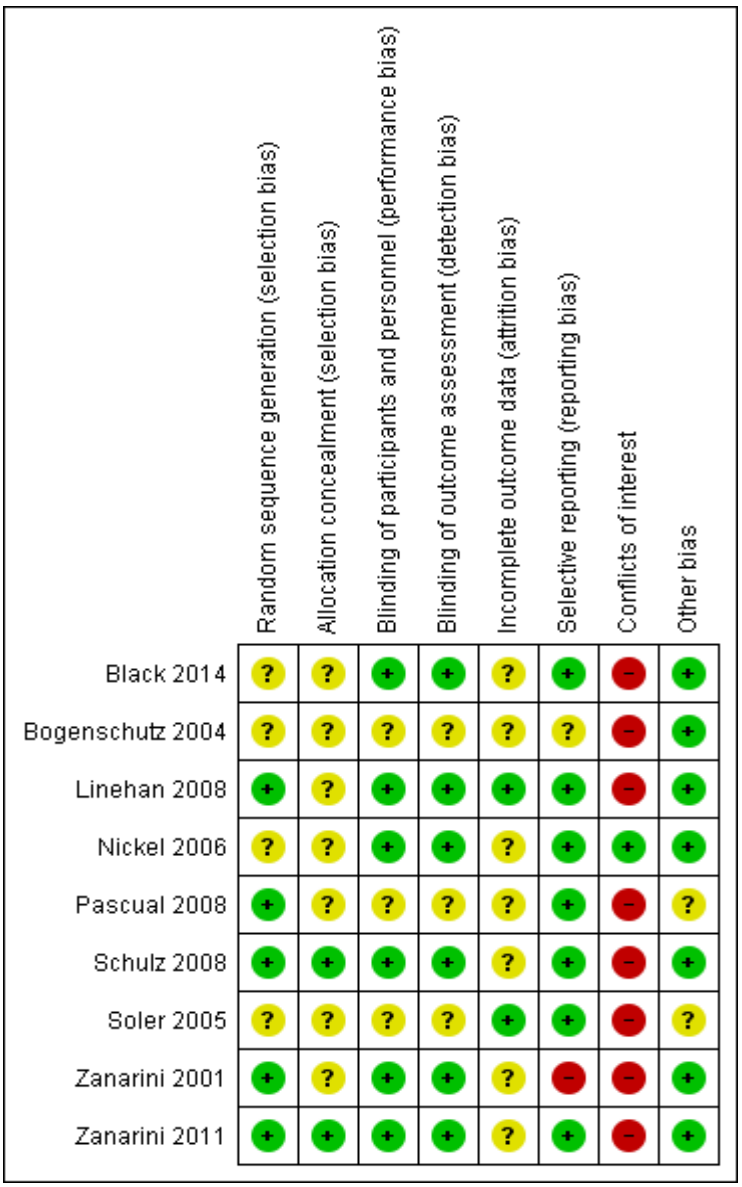

Figure 2. Cochrane Risk of Bias Summary for the included studies (Higgins et al., 2019).

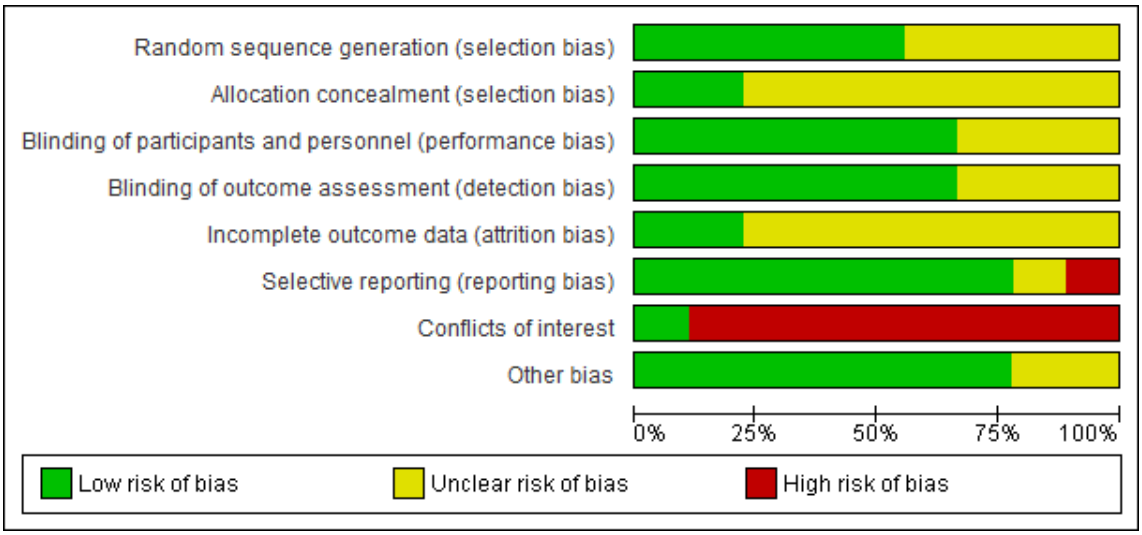

Figure 3. Cochrane Risk of Bias Graph for the included studies (Higgins et al., 2019).

3.4. Review of the evidence

The following sections will summarize the evidence currently available for each drug studied, mainly comparing its effect with placebo in terms of outcomes and adverse effects. The strengths and limitations of the studies will also be discussed. The appraisal of each study's findings, strengths and limitations is presented in Table 3.

Table 3. Assessment of included studies

Studies	Intervention	Main results[b] (intervention v. placebo)*	Strengths	Limitations
Zanarini et al., 2001	Olanzapine	• Lower SCL-90 Interpersonal Sensitivity, Depression, Anxiety and Anger/Hostility scores.	Long duration. Low dosage.	Small sample. Exclusion of men. High dropout rate.
Bogenschutz et al., 2004	Olanzapine	• Lower total CGI-BPD score. • Lower Inappropriate Anger (Item-Level) CGI-BPD score. • Lower HAM-D score (week 8).	Low dosage.	Small sample.
Soler et. al., 2005	Olanzapine[a]	• Lower HAM-D and HAM-A scores. • Decrease in the frequency of impulsive/aggressive behavior.	Use of DBT.	Excludes people with active comorbid disorders. Possible drug-drug interaction.
Nickel et al., 2006	Aripiprazole	• Greater rate of improvement in SCL-90-R scores (except somatization). • Lower HAM-D and HAM-A scores. • Lower scores on all scales of the State-Trait Anger Expression Inventory. • Long-term improvement in SCL-90-R scores (18 months)[c].	Use of a well-tolerated drug. Low dropout rate.	Small sample. Short duration.
Linehan et al., 2008	Olanzapine[a]	• Quicker improvement on OAS-M Irritability scores (week 7). • Physical aggression scores reduced more quickly (first 3 months)	Use of DBT. Use of a RRM.	Exclusion of men. Small sample.
Pascual et al., 2008	Ziprasidone	• No significant differences were found in any of the evaluated outcomes.	Use of psychotherapy.	High dropout rate. Possible drug-drug interaction.
Schulz et al., 2008	Olanzapine	• Lower total ZAN-BPD score (weeks 6 and 8). • Shorter time to reach 50% reduction in total ZAN-BPD score. • Lower Anger ZAN-BPD score. • Higher suicidal/self-mutilating behavior ZAN-BPD scores. • Improvements on OAS-M Irritability and SCL-90-R Hostility scores.	Big sample. Multicentered study.	No blinding to dose change. Insufficient titration of dose. Excludes people with active comorbid disorders.
Zanarini et al., 2011	Olanzapine	• Lower total ZAN-BPD score (weeks 2, 4, 6, 8 and 10) – 5-10 mg. • Shorter time to reach 50% reduction in total ZAN-BPD score – 5-10 mg. • Lower scores on the anger, affective instability, paranoid ideation or dissociation and suicidal/self-mutilating behavior items of ZAN-BPD – 2,5 mg (self-mutilation item) and 5-10 mg. • Lower OAS-M irritability and suicidality – 2,5 mg and 5-10 mg.	Big sample. Multicentered study.	Excludes people with active comorbid disorders.
Black et al., 2014	Quetiapine	• Improvement in ZAN-BPD total score – 150 mg. • Shorter time to reach 50% reduction in total ZAN-BPD score – 150 mg and 300 mg. • Lower OAS-M score – 150 mg and 300 mg.	Blinding to dose change. Low dosage.	Short duration. High dropout rate. Excludes people with active comorbid disorders.

* $p<0.05$. The between-group results presented have reached statistical significance.
[a] Olanzapine+DBT v. Placebo+DBT.
[b] These are the findings taken at endpoint, unless otherwise specified.
[c] Results reported in a different article (Nickel et al., 2007).
Abbreviations: SCL-90=Symptom Checklist-90, SCL-90-R= SCL-90 Revised, CGI=Clinical Global Impressions Scale, CGI-BPD=CGI modified for BPD, OAS-M=Overt Agression Scale Modified, ZAN-BPD=Zanarini Rating Scale for BPD, DBT=Dialectical Behavior Therapy, RRM= Random Regression Model, HAM-A=Hamilton Anxiety Rating Scale, HAM-D=Hamilton Depression Rating Scale.

3.4.1. Olanzapine v. Placebo

Olanzapine is the most well studied SGA for BPD. According to the findings in Table 3, it is apparent it is more efficacious against overall BPD symptoms than placebo through lower SCL-90, CGI-BPD and ZAN-BPD scores at a relatively low dose (Bogenschutz and George Nurnberg, 2004; Schulz et al., 2008; Zanarini and Frankenburg, 2001; Zanarini et al., 2011). When evaluating for specific symptoms, olanzapine appears to have a better effect than placebo on impulsiveness, irritability, depression and anxiety (Bogenschutz and George Nurnberg, 2004; Linehan et al., 2008; Schulz et al., 2008; Soler et al., 2005; Zanarini and Frankenburg, 2001; Zanarini et al., 2011).

The two studies with the biggest samples have not been able to find significant differences between ZAN-BPD scores at endpoint. However, they did find that olanzapine had a quicker effect than placebo when evaluating for time-to-treatment response (Schulz et al., 2008; Zanarini et al., 2011). Zanarini et al. (2011) managed to evaluate two groups with olanzapine on different doses: one group with 2.5 mg and another with 5-10 mg. This study has shown greater results with 5-10 mg of olanzapine than with 2.5 mg (Zanarini et al., 2011). This multicenter RCT also managed to lower patient dropout by contacting the subjects via telephone (Zanarini et al., 2011). In contrast, Schulz et al. (2008) found a contradictory result with Zanarini et al. (2011), suicidal behavior and self-injury scores were significantly worse on olanzapine than with placebo (Schulz et al., 2008). This finding is congruent with other studies that found a higher nonsignificant reduction of these behaviors in the placebo condition (Linehan et al., 2008; Soler et al., 2005). Linehan et al. (2008) proposes that these findings might be explained by the hypothesis that both aggressiveness and self-injury serve the function to regulate irritability, and as one goes down, the other has a slower reduction (Linehan et al., 2008). While this is something important to consider in future studies, the small samples (Linehan et al., 2008; Soler et al., 2005), high dropout rate and insufficient titration of dose (Schulz et al., 2008) do not give much confidence about their findings and should therefore be interpreted with caution.

There are two clinical trials that studied the effect of olanzapine with DBT in both groups: Soler et al. (2005) and Linehan et al. (2008). Since DBT is one of the recommended psychotherapeutic options for BPD (National Collaborating Centre for Mental Health, 2009; Oud et al., 2018), these findings are interesting in indicating that olanzapine might

be beneficial in reducing impulsiveness and aggressive behavior and therefore potentiate psychotherapeutic approaches. Furthermore, use of DBT has shown to be an effective strategy to lower dropout rates (Linehan et al., 2008; Soler et al., 2005).

Even though olanzapine is effective, it also has some relevant side effects when compared with placebo. Overall, the most common adverse effect found was weight gain (Bogenschutz and George Nurnberg, 2004; Linehan et al., 2008; Schulz et al., 2008; Soler et al., 2005; Zanarini and Frankenburg, 2001; Zanarini et al., 2011), followed by sedation (Linehan et al., 2008; Schulz et al., 2008; Zanarini et al., 2011), higher cholesterol levels (Schulz et al., 2008; Soler et al., 2005; Zanarini et al., 2011) and higher prolactin levels (Schulz et al., 2008; Zanarini et al., 2011).

3.4.2. Aripiprazole v. Placebo

Nickel et al. decided to study aripiprazole in BPD using a fixed-dose (15 mg) for 8 weeks, and then evaluated their patients after the experiment for 18 months (Nickel et al., 2007; Nickel et al., 2006). As it is described in Table 3, aripiprazole is more effective than placebo regarding overall self-reported BPD symptoms and lowers aggressiveness, depression and anxiety at 8 weeks (Nickel et al., 2006). At 18 months, aripiprazole showed a significant reduction when compared with placebo in the SCL-90-R scores, however, these findings should be interpreted with caution, since the blind was broken when the experiment ended (at 8 weeks) (Nickel et al., 2007).

There were no significant extrapyramidal symptoms or weight gain found in those studies comparatively with placebo (Nickel et al., 2007; Nickel et al., 2006).

3.4.3. Ziprasidone v. Placebo

The effects of ziprasidone in BPD were assessed by Pascual et al. Unfortunately, no significant differences between this drug and placebo were found in any of the evaluated outcomes (Pascual et al., 2008). This lack of significance in results might have been due to their high dropout rate, even though they implemented nonspecific psychotherapy to prevent that (Pascual et al., 2008).

The main adverse effects present with ziprasidone were sedation and dizziness (Pascual et al., 2008).

3.4.4. Quetiapine v. Placebo

Quetiapine is studied in the most recent RCT included in this review. In this clinical trial by Black et. al (2014), there were two groups with quetiapine – one with a 150 mg and one with 300 mg (Black et al., 2014). This study shows that quetiapine, much like the others, is effective in reducing BPD severity quicker than placebo and it also reduces aggressiveness (Black et al., 2014). Surprisingly, according to Table 3, administering 150 mg of quetiapine is associated with better outcomes than taking 300 mg (Black et al., 2014). This finding might suggest that a low dose is more optimal than a moderate one, but it is too soon to reach that conclusion with one study with such a short duration. The authors unexpectedly did not find significant differences on levels of depression and impulsivity between quetiapine and placebo.

Both doses of quetiapine were associated with higher weight gain (Black et al., 2014).

4. Discussion

4.1. Summary and appraisal of available evidence

This review set out to update and qualitatively assess the evidence regarding use of SGAs in BPD patients. These findings corroborate those of Lieb et al. (2010). In general, the results favor using SGAs in BPD, especially when aggressive and impulsive symptoms are present. Additionally, quetiapine appears to be another option to use for BPD, although further studies are needed. However, between their review in 2010 and this one, only one new RCT who met the inclusion criteria was reported (Black et al., 2014). Lieb et al. (2010) stated in their review that these RCTs did not include inpatients and were too strict on their exclusion criteria on the terms that patients with active comorbidities including mood and anxiety disorders were excluded (Lieb et al., 2010). Therefore, extrapolating these results to those patients is inadequate. This review, by analyzing the quality of the included studies, has found it would certainly be important to include inpatients, and people with other mental disorders since comorbidities are very frequent in BPD. Furthermore, it would also be interesting to find out the effects of SGAs in acutely suicidal patients, which were also excluded in these studies (Lieb et al., 2010).

These SGAs have proven to have mild to moderate adverse effects, with olanzapine having the most side effects and aripiprazole having the least. However, none of these studies reported extrapyramidal symptoms or movement disorders, which puts SGAs at

an advantage against typical antipsychotics (Lieb et al., 2010). However, something important to account for and investigate further is the contradictory effects of Olanzapine on suicidality and self-injurious behavior (Linehan et al., 2008; Schulz et al., 2008; Zanarini et al., 2011).

It appears the outcomes evaluated by these studies are becoming more and more standardized, as the latest three included clinical trials (Black et al., 2014; Schulz et al., 2008; Zanarini et al., 2011). However, it would also be important for future studies to add and evaluate more objective measures (e.g. emergency unit visits, suicide attempts) and compare those with placebo.

Overall, these RCTs suffered from moderate to high dropout rates, which can potentiate attrition bias. Specialized psychotherapy (DBT) and calling the patients for additional checkups have been used to lower patient dropout with some success (Linehan et al., 2008; Soler et al., 2005; Zanarini et al., 2011). Further research should strive to implement measures like these to have longer follow-ups without high dropout rates and assess the long-term effects of SGAs.

Using psychotherapeutic approaches like DBT in both groups is something that should be done in the future, since it is of the upmost importance to evaluate the combination of pharmacotherapy with psychotherapy to obtain the best treatment possible. Ideally, future research should compare various SGAs in a multicenter study, while applying DBT or other specific psychotherapies in all groups.

4.2. Limitations of this review

This review had several limitations. Firstly, this review doesn't include a meta-analysis due to the highly heterogeneous data presented in each study. Another limitation is that the main findings were only qualitatively assessed by being statistically significant between groups and it did not take effect sizes into account.

4.3. Conclusions

In conclusion, SGAs can be beneficial for BPD patients and even serve as a co-treatment with psychotherapy. However, further research is needed to compare between different SGAs and establish the evidence necessary for recommendation.

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Conflicts of interest

The authors declare there is no conflict of interest. This is an independent review.

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Supplementary file 1

Characteristics of included studies

Zanarini 2001

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Tablets were supplied in numbered bottles containingdrug or placebo as determined by a random number sequence." (p. 850)
Allocation concealment (selection bias)	Unclear risk	Insufficient data.
Blinding of participants and personnel (performance bias)	Low risk	"Both subjects and clinicians were blinded to olanzapine/placebo assignment. The blind was broken afterthe acquisition of all endpoint data for all subjects." (p. 850)
Blinding of outcome assessment (detection bias)	Low risk	"Both subjects and clinicians were blinded to olanzapine/placebo assignment. The blind was broken afterthe acquisition of all endpoint data for all subjects." (p. 850)
Incomplete outcome data (attrition bias)	Unclear risk	"89.5% (17/19) and 88.9% (8/9) of the olanzapine treated and placebo-treated subjects remained in the study through week 4, 63.2% (12/19) and 66.7% (6/9) remained for the first12 weeks, and 42.1% (8/19) and 44.4% (4/9) remained through week 20. However, a substantially but not significantly higher percentage of olanzapine-treated subjects than placebo-treated subjects (42.1% [N = 8] vs. 11.1% [N = 1]) remained in the study all 24 weeks (Fisher exact test = 0.195)." (p. 851) Even though there were not statistically significant differences between the two groups interms of loss of follow-up, the study's small sample size raises some doubts.
Selective reporting (reporting bias)	High risk	"Due to the small number of subjects, results pertaining to secondary outcome measureswill not be reported." (p. 851)
Conflicts of interest	High risk	Possible conflict of interest: "Supported, in part, by a grantfrom Eli Lilly." (p. 849)
Other bias	Low risk	No other sources of bias found.

Bogenschutz 2004

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly assigned in equal numbers to 12weeks of double-blind treatment with olanzapine (dose range, 2.5–20 mg) or placebo." (p. 105)
Allocation concealment (selection bias)	Unclear risk	Insufficient data.
Blinding of participants and personnel (performance bias)	Unclear risk	"Patients were randomly assigned in equal numbers to 12weeks of double-blind treatment with olanzapine (dose range, 2.5–20 mg) or placebo." (p. 105)
Blinding of outcome assessment (detection bias)	Unclear risk	"Patients were randomly assigned in equal numbers to 12weeks of double-blind treatment with olanzapine (dose range, 2.5–20 mg) or placebo." (p. 105)
Incomplete outcome data (attrition bias)	Unclear risk	"Thirty-five patients completed at least 2 weeks of treatment and at least 1 postbaseline assessment and hence were included in the endpoint analysis. Twenty-three patients completed the full 12 weeks of the trial. There were no hospitalizations, suicide attempts, or other serious adverse events in either group. Dropouts by timepoint are summarized in Figure 1. Reasons for early termination were as follows: lost to follow-up, 2 (10%) in the olanzapine group and 5 (25%) in the placebo group; lack of efficacy, 2 (10%) ineach group; weight gain, 2 (10%) in the olanzapine group; sedation, 2 (10%) in the olanzapine group; and patient violation of protocol, 2 (10%) in the olanzapine group." (p. 106)
Selective reporting (reporting bias)	Unclear risk	Insufficient data.
Conflicts of interest	High risk	"Supported by a grant from Eli Lilly and Co., Indianapolis, Ind." (p. 104)
Other bias	Low risk	No other sources of bias found.

Soler 2005

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"They were then randomly assigned to receive dialectical behavior therapy plus either olanzapine or placebo on a 1:1ratio." (p. 1222)
Allocation concealment (selection bias)	Unclear risk	Insufficient data.
Blinding of participants and personnel (performance bias)	Unclear risk	"We carried out a singlecenter, randomized, double-blind, placebo-controlled study to compare the efficacy and safety of dialectical behavior therapy plus olanzapine or placebo in patients with borderline personality disorder." (p. 1222)
Blinding of outcome assessment (detection bias)	Unclear risk	"We carried out a singlecenter, randomized, double-blind, placebo-controlled study to compare the efficacy and safety of dialectical behavior therapy plus olanzapine or placebo in patients with borderline personality disorder." (p. 1222)
Incomplete outcome data (attrition bias)	Low risk	"Neither dialectical behavior therapy intervention time nor dropout rates differed significantly between the two groups (eight of the 30 patients who received olanzapine versus 10of the 30 who received placebo dropped out before the end of the study) (Table 1)." (p. 1223)
Selective reporting (reporting bias)	Low risk	The authors present the results of all of the outcomes they assessed.
Conflicts of interest	High risk	"Supported by grants from the Fondo de Investigación Sanitaria (Ministry of Health, Spain) and from Eli Lilly and Co.Madrid." (p. 1222)
Other bias	Unclear risk	"Patients could continue treatment with benzodiazepines, anti-depressants, and mood stabilizers, but doses could not be modified." (p. 1222) Possible drug-drug interaction.

Nickel 2006

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The random assignment was carried out confidentially by the clinic administration..." (p. 835) "Tablets were supplied in numbered boxes." (p. 835)
Allocation concealment (selection bias)	Unclear risk	"The random assignment was carried out confidentially by the clinic administration..." (p. 835) "Tablets were supplied in numbered boxes." (p. 835)
Blinding of participants and personnel (performance bias)	Low risk	"Both the subjects and the clinicians were blinded regardingthe assignment of aripiprazole or placebo." (p. 835)
Blinding of outcome assessment (detection bias)	Low risk	"Both the subjects and the clinicians were blinded regardingthe assignment of aripiprazole or placebo." (p. 835)
Incomplete outcome data (attrition bias)	Unclear risk	"Five subjects who missed more than two weekly evaluations dropped out." (p. 835)
Selective reporting (reporting bias)	Low risk	The authors present the results of all of the outcomes they assessed.
Conflicts of interest	Low risk	"The study was conducted independent of any institutional influence and was not funded." (p. 835)
Other bias	Low risk	No other sources of bias found.

Schulz 2008

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"All participants, study site personnel and investigators were masked to randomisation codes." (p. 485)
Allocation concealment (selection bias)	Low risk	"All participants, study site personnel and investigators were masked to randomisation codes." (p. 485)
Blinding of participants and personnel (performance bias)	Low risk	"The study consisted of a 2−14 day screening period followedby a 12-week double-blind acute treatment period." "All participants, study site personnel and investigators were masked to randomisation codes." (p. 485)
Blinding of outcome assessment (detection bias)	Low risk	"The study consisted of a 2−14 day screening period followedby a 12-week double-blind acute treatment period." "All participants, study site personnel and investigators were masked to randomisation codes." (p. 485)
Incomplete outcome data (attrition bias)	Unclear risk	"Rates of discontinuation from the 12-week acute phase were48.4% (75/ 155) for the olanzapine group and 38.4% (61/159) for the placebo group, which were not statistically significantly different. Of those who discontinued, 11.0% (17/155) of people in the olanzapine group and 11.3% (18/159) in the placebo group discontinued due to an adverse event, while 16.1% (25/155) in the olanzapine group and 9.4% (15/159) in the placebo group discontinued due to participant decision. The mean times to discontinuation were 64.5 days (s.d.=35.6) for olanzapine and 67 days (s.d.=28.7) for placebo. Rates of discontinuation from the study by visit varied from 0−12%, with the highest rates occurring at the 4- and 6-week time points in both the olanzapine (12% and 10.4%) and placebo (10.3% and 9.4%) treatment groups." (p.487-488)
Selective reporting (reporting bias)	Low risk	The authors present the results of all of the outcomes they assessed.
Conflicts of interest	High risk	"This study was sponsored by Eli Lilly. S.C.S. has received honorarium from Eli Lilly, AstraZeneca and Bristol-Meyers Squibb; grant fees from Eli Lilly, AstraZeneca, Abbott, MIND Institute and the NIMH; and consultation fees from Eli Lilly, AstraZeneca and Vanda. H.C.D., Q.T., Y.T., D.L. and S.C. are employed by Lilly Research Laboratories." (p. 485)
Other bias	Low risk	No other sources of bias found.

Pascual 2008

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were then randomly assigned to ziprasidone or placebo (1:1 ratio). Randomization was performed by blocksof 4 generated using the SPSS software package (SPSS Inc., Chicago, Ill.)." (p. 2)
Allocation concealment (selection bias)	Unclear risk	Insufficient data.
Blinding of participants and personnel (performance bias)	Unclear risk	"This was a single-center, randomized, double-blind, placebo-controlled clinical trial consisting of 2 phases…" (p. 1)
Blinding of outcome assessment (detection bias)	Unclear risk	"This was a single-center, randomized, double-blind, placebo-controlled clinical trial consisting of 2 phases…" (p. 1)
Incomplete outcome data (attrition bias)	Unclear risk	"No significant differences were detected between the 2 groups in dropout rates; 56.7% (17/30) in the ziprasidone group and 46.7% (14/30) in the placebo group did not complete the study. The reasons for withdrawal in the ziprasidone group were need of psychiatric hospitalization (N = 4), adverse events/patient decision (N = 9), clinician decision/insufficient treatment effect (N = 3),and other reasons (N = 1). In the placebo group, the reasons for withdrawal were need of psychiatric hospitalization (N = 3), patient decision (N = 4), and clinician decision/lack of efficacy(N = 7)." (p. 4)
Selective reporting (reporting bias)	Low risk	The authors present the results of all of the outcomes they assessed.
Conflicts of interest	High risk	"This study was supported by grants from the Fondo de Investigación Sanitaria (Ministry of Health, Spain), the REM-TAP Network, and Pfizer, Madrid, Spain." (p. 1)
Other bias	Unclear risk	"Patients were allowed to continue treatment with benzodiazepines, antidepressants, and mood stabilizers if they had been initiated prior to inclusion, but doses could notbe modified during the study." (p. 2)

Linehan 2008

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Each tablet contained either 5 mg of olanzapine or matchinginert placebo as determined by a random number sequence."(p. 1000)
Allocation concealment (selection bias)	Unclear risk	Insufficient data.
Blinding of participants and personnel (performance bias)	Low risk	"Patients, psycho therapists, pharmacotherapist, and assessment interview ers were kept naive to medication assignment. At the end of the study, the pharmacotherapistand interviewers were unable to guess group assignment above chance ..." (p. 1000)
Blinding of outcome assessment (detection bias)	Low risk	"Patients, psycho therapists, pharmacotherapist, and assessment interview ers were kept naive to medication assignment. At the end of the study, the pharmacotherapistand interviewers were unable to guess group assignment above chance ..." (p. 1000)
Incomplete outcome data (attrition bias)	Low risk	"Eight patients (33%: 4 olanzapine, 4 placebo) dropped out ofDBT and consequently were not continued on medication. Five of those (21% of total) also dropped out of the assessment sequence before the final assessment; 4 (17%) missed the time-2 and time-3 assessments and 1 missed only the time-3 assessment. One patient, assigned to the olanzapine condition, dropped out due to pregnancy (at week10). In addition, 1 patient assigned to the olanzapine condition was removed from the study at week 7 due to psychotic symptoms (she was not counted as a dropout). Although she was subsequently treated effectively with a higher dose of olanzapine, no further assessments were conducted. There was no statistically significant between-condition difference in dropout rate." (p. 1001)
Selective reporting (reporting bias)	Low risk	The authors present the results of all of the outcomes they assesed.
Conflicts of interest	High risk	"This research was supported by a grant from Eli Lilly andCo,… " (p. 999)
Other bias	Low risk	No other sources of bias found.

Zanarini 2011

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients who met enrollment criteria at visit 2 were randomly assigned in a 1:1:1 ratio, stratified by study center, to receive treatment with olanzapine 2.5 mg/d, olanzapine 5–10 mg/d, or placebo. All patients, study site personnel, and investigators were blinded to randomization codes." (p. 1354)
Allocation concealment (selection bias)	Low risk	"Patients who met enrollment criteria at visit 2 were randomly assigned in a 1:1:1 ratio, stratified by study center, to receive treatment with olanzapine 2.5 mg/d, olanzapine 5–10 mg/d, or placebo. All patients, study site personnel, and investigators were blinded to randomization codes." (p. 1354)
Blinding of participants and personnel (performance bias)	Low risk	"Patients who met enrollment criteria at visit 2 were randomly assigned in a 1:1:1 ratio, stratified by study center, to receive treatment with olanzapine 2.5 mg/d, olanzapine 5–10 mg/d, or placebo. All patients, study site personnel, and investigators were blinded to randomization codes." (p. 1354)
Blinding of outcome assessment (detection bias)	Low risk	"Patients who met enrollment criteria at visit 2 were randomly assigned in a 1:1:1 ratio, stratified by study center, to receive treatment with olanzapine 2.5 mg/d, olanzapine 5–10 mg/d, or placebo. All patients, study site personnel, and investigators were blinded to randomization codes." (p. 1354)
Incomplete outcome data (attrition bias)	Unclear risk	"Over 60% of the subjects in each study group completed thetrial (Figure 1). Overall, no statistically significant between-group differences were observed with regard to patient disposition." (p. 1355)
Selective reporting (reporting bias)	Low risk	The authors present the results of all of the outcomes they assesed.
Conflicts of interest	High risk	"Dr Zanarini has received grant/research support from EliLilly. Dr Schulz has been a consultant for Eli Lilly and hasreceived grant/research support from Eli Lilly and AstraZeneca." (p. 1361)
Other bias	Low risk	No other sources of bias found.

Black 2014

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Participants who met enrollment criteria at both visits 1 and2 were randomly assigned to receive treatment with 150 mg/day of extended-release quetiapine, 300 mg/day of extended-release quetiapine, or placebo. Participants, site personnel, and investigators were blind to treatment group assignment." (p. 1175)
Allocation concealment (selection bias)	Unclear risk	Insufficient data.
Blinding of participants and personnel (performance bias)	Low risk	"Participants who met enrollment criteria at both visits 1 and2 were randomly assigned to receive treatment with 150 mg/day of extended-release quetiapine, 300 mg/day of extended-release quetiapine, or placebo. Participants, site personnel, and investigators were blind to treatment group assignment." (p. 1175)
Blinding of outcome assessment (detection bias)	Low risk	"Participants who met enrollment criteria at both visits 1 and2 were randomly assigned to receive treatment with 150 mg/day of extended-release quetiapine, 300 mg/day of extended-release quetiapine, or placebo. Participants, site personnel, and investigators were blind to treatment group assignment." (p. 1175)
Incomplete outcome data (attrition bias)	Unclear risk	"Of all participants assigned to a treatment group, 64 (67%) completed the study, 23 of them in the placebo group, 22 in the low-dosage quetiapine group, and 19 in the moderate dosage quetiapine group. Eight participants dropped out before a postbaseline assessment. Risk of discontinuation was higher among participants who received quetiapine, but the differences from placebo were not significant for either dosage group. Illness severity (measured by the Zanarini scale total score as a time-varyingpredictor) was not associated with discontinuation. Risk of discontinuation increased with severity of any adverse event (hazard ratio=1.74, p=0.018). Sedation was predictive of discontinuation (hazard ratio=1.77, p=0.025)." (p. 1176)
Selective reporting (reporting bias)	Low risk	The authors present the results of all of the outcomes they assesed.
Conflicts of interest	High risk	"Supported by a grant from AstraZeneca to Dr. Schulz, with subcontracts to Drs. Black and Zanarini." (p. 1181)
Other bias	Low risk	No other sources of bias found.

Anexos

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page and paragraph/ table #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both. **- MANDATÓRIO**	p. 1 See Title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. **– SEGUIR RECOMENDAÇÕES DA REVISTA**	p. 1 See Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. **– MANDATÓRIO** ***O rationale corresponde à justificação da importância da revisão sistemática***	p. 3 “A previous systematic review of Randomized Controlled Trials (RCTs) made by Lieb et al. (2010) showed that both olanzapine and aripiprazole reduced the core symptoms of BPD when compared with placebo, most notably impulsivity, psychotic symptoms and interpersonal hardships (Lieb et al., 2010). However, the evidence was not robust, and they recommended further research (Lieb et al., 2010). Since more than ten years have passed, new findings may be available for review. It is important to assess the efficacy of SGAs because pharmacotherapy should be targeted for specific symptoms of BPD, and to avoid polypharmacy, there is a need to produce high quality evidence-based decisions in treating these patients (Lieb et al., 2010).”
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). **- MANDATÓRIO**	p. 3 “The aim of this systematic review is to update on the state of the art regarding the effects of SGAs in people with BPD through a qualitative assessment of RCTs.”
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. **– FACULTATIVO**	Non applicable
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as	p. 3 “For this systematic review, RCTs studying atypical antipsychotics in patients with diagnosed BPD were included up to March 3rd,

		criteria for eligibility, giving rationale. **– MANDATÓRIO** ***É altamente recomendado, de acordo com as boas práticas da Cochrane, que não sejam aplicados critérios de exclusão baseados na língua e/ou data de publicação dos estudos.***	2021. Inclusion criteria are as follows: being a RCT, having an intervention group consisting of an atypical antipsychotic and having patients with BPD. Studies were excluded if they had no placebo group as comparison. There were no language or data restrictions applied.”
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. **– MANDATÓRIO** ***Em consonância com as boas práticas da Cochrane, é mandatório que se verifique pesquisa em pelo menos duas bases de pesquisa bibliográfica (idealmente, deverão ser pesquisadas duas bases generalistas e uma específica da área). No caso de revisões sistemáticas de estudos experimentais/ensaios clínicos aleatorizados, é altamente recomendado que uma das bases pesquisadas corresponda à CENTRAL ou a bases de ensaios clínicos como a ClinicalTrials.gov.*** ***Estudos de revisão da literatura em que a pesquisa decorra numa única base de dados não serão classificados como revisões sistemáticas.***	p. 3 “A search was performed in the following electronic databases: MEDLINE, SCOPUS, ISI Web of Knowledge and PsycInfo. The search query included the keywords “borderline personality disorder”, “Antipsychotic Agents”, “Aripiprazole”, “Olanzapine”, “Quetiapine”, “controlled trial”, “RCT” and “placebo”. In order to obtain an evidence-based search strategy to find clinical trials, two InterTASC filters for RCTs were used in MEDLINE and PsycINFO (Eady et al., 2008; Lefebvre et al., 2021). Table 1 presents the search strategy in more detail. Additionally, some references were retrieved from the last review made by Lieb et. al (2010).” See Table 1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. **– MANDATÓRIO** ***A query de pesquisa deve ser obrigatoriamente disponibilizada. A utilização de filtros de pesquisa da InterTASC é altamente recomendada (https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home)***	See Table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). **– MANDATÓRIO** ***As fases de selecção dos estudos primários devem ser descritas. Em consonância com as boas práticas da Cochrane, é mandatório que o processo de selecção envolva duas fases (fase de rastreio, em que os registos são seleccionados por título e abstract, e fase de inclusão, na qual se procede à leitura integral dos full texts). Em cada uma destas fases, o processo de selecção deve mandatoriamente envolver dois investigadores actuando de forma independente.***	p. 5 “Studies were first screened through reading of titles and abstracts. After the screening, full-texts of eligible articles were retrieved and read thoroughly before deciding to include or exclude. The authors of the studies were contacted to retrieve some full-texts. This process was performed independently by two reviewers. In case of disagreement, consensus did the resolution.”
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. **– MANDATÓRIO** ***Trata-se de descrever de que forma se procedeu à extracção de dados dos estudos primários. Em consonância com as boas práticas da Cochrane, tal***	p. 5 “Data from each study regarding study design, participants, methods, intervention, outcomes and main findings were collected through a spreadsheet form. The outcomes of interest are the various scales used to measure BPD symptomology (e.g. ZAN-BPD scale, CGI-

		processo deverá envolver dois investigadores de forma independente.	BPD scale, OAS-M scale, …). The main findings of each study consist of statistically significant results ($p < 0.05$) between-groups. Within-group differences were not assessed. This process was performed independently by two reviewers. In case of disagreement, consensus did the resolution."
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. **– MANDATÓRIO** ***Trata-se de descrever as variáveis para as quais foi obtida informação.***	p. 5 "Data from each study regarding study design, participants, methods, intervention, outcomes and main findings were collected through a spreadsheet form. The outcomes of interest are the various scales used to measure BPD symptomology (e.g. ZAN-BPD scale, CGI-BPD scale, OAS-M scale, …). The main findings of each study consist of statistically significant results ($p < 0.05$) between-groups. Within-group differences were not assessed. This process was performed independently by two reviewers. In case of disagreement, consensus did the resolution."
Risk of bias in individual studies / Risk of bias across studies	12/ 15	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. **– MANDATÓRIO** ***Em todas as revisões sistemáticas, deverá existir um processo de avaliação da qualidade dos estudos primários. No caso de revisões sistemáticas de estudos experimentais/ensaios clínicos aleatorizados, a aplicação dos critérios de risco de viés (Risk of Bias) da Cochrane é altamente recomendada. No caso de revisões sistemáticas de estudos observacionais, poderão ser seguidos os critérios ROBINS ou os critérios dos National Institutes of Health (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).***	p. 5 "Risk of bias of each study was performed according to the Cochrane Risk of Bias Tool (Higgins et al., 2019) using the software program RevMan. This Risk of Bias Tool assesses the following domains: random allocation sequence, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, conflicts of interest and other bias (Higgins et al., 2019). This assessment was only done at the overall study level and did not account for the risk of bias for each specific outcome. This process was only done by the author."
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). **– FACULTATIVO. APENAS NECESSÁRIO SE FOR FEITA META-ANÁLISE**	Non applicable. Not a meta-analysis.
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis. **– FACULTATIVO. APENAS NECESSÁRIO SE FOR FEITA META-ANÁLISE**	Non applicable. Not a meta-analysis.
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. **– FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE**	Non applicable. Not a meta-analysis.

PRISMA 2009 Checklist

RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. **– MANDATÓRIO**	p.6 “The included studies were all double-blinded RCTs in an outpatient setting and used an intention-to-treat analysis (ITT) to assess their outcomes. While the majority of studies used variable doses of antipsychotic, three used fixed doses (Black et al., 2014; Nickel et al., 2006; Zanarini et al., 2011). Two RCTs applied DBT in both groups (Linehan et al., 2008; Soler et al., 2005), while another used nonspecific psychotherapy (Pascual et al., 2008). Most of the included studies used a last observation carried forward (LOFC) analysis for the participants who dropped out (Black et al., 2014; Bogenschutz and George Nurnberg, 2004; Pascual et al., 2008; Schulz et al., 2008; Soler et al., 2005; Zanarini et al., 2011). It should be noted Nickel et al. (2006) reported in a different article the results of their outcomes 18 months after the experiment (Nickel et al., 2007).” See Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. **– MANDATÓRIO**	p. 8 “Table 2 describes the main characteristics of each study. As it can be observed, most of their inclusion criteria required a diagnosis of BPD according to the DSM-IV criteria (American Psychiatric Association, 2000) and having at least a moderate severity of illness, except in these clinical trials: Zanarini et al. (2001), Bogenschutz et al. (2004) and Nickel et al. (2006)…” See Table 2
Risk of bias within and across studies	19/ 22	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). **– MANDATÓRIO**	p. 9-10 “The risk of bias in each study was assessed and can be observed in Figure 2. According to the risk of bias graph presented in Figure 3, these studies have in general a low risk of bias due to blinding and selective reporting when it comes to outcomes reported in the study. However, eight out of nine studies had a high risk of conflict of interest (most researchers received grants or research support from pharmaceutical companies), which may have an influence on their findings. Furthermore,

			numerous studies provided insufficient data regarding allocation concealment. Moderate to high dropout rates in these trials are to be expected, so there is higher risk for attrition bias…" See Figures 2 and 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. **– FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE**	Non applicable. Not a meta-analysis.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency. **– FACULTATIVO. MANDATÓRIO APENAS SE FOR FEITA META-ANÁLISE**	Non applicable. Not a meta-analysis.
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). **– FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE**	Non applicable. Not a meta-analysis.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). **– MANDATÓRIO**	See p. 14 "4.1. Summary and appraisal of available evidence"
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). **– MANDATÓRIO**	See p. 15 "4.2. Limitations of this review"
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research. **– MANDATÓRIO**	See p. 15 "4.3. Conclusions"
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. **– SEGUIR RECOMENDAÇÕES DA REVISTA**	See p. 16 "Funding"

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

PSYCHIATRY RESEARCH

AUTHOR INFORMATION PACK

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