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TITLE PAGE

Title;

Optimal dose of brexpiprazole for augmentation therapy of antidepressant-refractory depression: a systematic review and dose-effect meta-analysis

A short running title;

Dose of brex augmentation for MDD (33 characters including spaces)

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Primary = Neuropsychopharmacology; secondary = general topics in psychiatry and related fields.

ABSTRACT: (247 words)

Background:

Brexpiprazole augmentation is an effective treatment strategy for antidepressant-refractory depression, but its optimal dosage remains unclear.

Aims:

To find the optimal dosage of brexpiprazole as augmentation of other antidepressants.

Methods:

We searched multiple electronic databases (from inception to September 16th, 2021) to identify double-blind, randomized placebo-controlled fixed-dose trials evaluating brexpiprazole augmentation therapy in adults (≥18 years old, both genders) with major depressive disorder not adequately responding to one or more antidepressant treatment. Our outcomes of interest at 8 weeks (range 4–12 weeks) were efficacy (treatment response defined as 50% or greater reduction in depression severity), tolerability (dropouts due to adverse effects) and acceptability (dropouts for any reason). We performed a random-effects, one-stage dose-effect meta-analysis with restricted cubic splines.

Results:

Six studies met the inclusion criteria, including 1,671 participants in total. The dose-efficacy curve showed an increase up to doses around 2 mg (odds ratio [OR] 1.52, 95% confidence interval [CI] 1.12-2.06) and then a decreasing trend through the higher licensed dose up to 3 mg (OR 1.40, 95%CI 0.95-2.08). The shape of the dose-tolerability curve was comparable to that of the efficacy and the dose-acceptability curve showed a monotonic increasing trend but both had wide confidence bands.

Conclusions:

One to two mg of brexpiprazole as augmentation treatment may achieve an optimal balance between efficacy, tolerability, and acceptability in the acute treatment of antidepressant-refractory depression. However, the small number of included studies limit the reliability of the results. Further research is required to validate the findings.

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FIVE KEY WORDS:

Depressive Disorder, Treatment-Resistant; Antipsychotic Agents; Brexpiprazole; Dose-Response Relationship, Drug; Meta-Analysis;

TEXT (3030 words)

INTRODUCTION

Major depressive disorder (MDD) is one of the leading causes of disability worldwide.[1] Available evidence suggests that the combination of pharmacotherapy and psychotherapy seems to be the best treatment option in the short-term[2], and delivery of psychotherapy as part of the initial treatment seems to be the optimal strategy to achieve sustained response in the long term.[3] In the clinical settings, however, where psychotherapy is often not sufficiently available,[4] pharmacotherapy is a common treatment choice. Although several effective antidepressants are available, [5] only about one-third of patients achieve symptomatic remission with the first antidepressant treatment [6,7] and treatment of those with inadequate response remains a critical clinical question. Previous studies suggest that treatment-resistant depression accounts for as many as one-third of MDD patients, [8,9] though the prevalence estimate is subject to the definition of treatment-resistance, which is diverse and heterogeneous. [10] In such cases, clinical guidelines recommend considering other pharmacotherapy strategies, psychotherapies[11] and neuromodulations[12]. Pharmacotherapy strategies include dose-escalation of the first antidepressant, switching to another antidepressant, combination with another antidepressant, or augmentation with a second agent other than antidepressants. [13] Recent meta-analyses showed no evidence of clinical benefits of dose-escalation, [14–16] or switching antidepressants, [17] while benefits of combining different types of antidepressants[18] and pharmacological augmentation with various non-antidepressant agents have been confirmed.[19] Atypical antipsychotics are commonly recommended as augmentation by many guidelines.[20] Brexpiprazole is a partial agonist of dopamine D2 receptors and serotonin 5HT-1A receptors, and an antagonist of serotonin 5HT-2A receptors.[21] It was approved as a monotherapy for schizophrenia and as an adjunctive therapy for MDD in the United States in 2015. It was then approved for schizophrenia treatment in Canada and Australia in 2017, in Japan in 2018, and in Europe in 2018. It was approved as an adjunctive therapy for MDD in Canada in 2019.[22] It is classified as a serotonin-dopamine activity modulator, a novel class of atypical antipsychotics, together with its predecessor, aripirazole. Brexpiprazole has less intrinsic activity at D2 receptors than aripiprazole and it is expected that brexpiprazole similar efficacy and improved tolerability (eg, potentially less akathisia) compared to aripiprazole. [21] The dose range of brexpiprazole augmentation ranges from 0.5 to 3 mg. [23] A recent meta-analysis confirmed brexpiprazole to be an effective drug, suggesting that higher doses were associated with lower response rates as well as more adverse events. [24,25] Understanding the dose-effect relationship is therefore important to enable clinicians to use brexpiprazole augmentation effectively and safely. We summarized the currently available evidence with the use of dose-effect meta-analysis to inform this clinical question.

OBJECTIVES

To investigate the dose-effect relationship of brexpiprazole as an augmentation agent for treating MDD with inadequate response to antidepressant therapy.

METHODS

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline. [26] The protocol was prospectively registered in PROSPERO (CRD42021273374) and can be found in the appendix (eAppendix1).

Data sources

Criteria for considering studies for this review

Types of studies

To examine dose-effect relationships, we included all double-blind randomized controlled trials that compared two or more doses of brexpiprazole as augmentation of antidepressant therapy within a trial. We regarded placebo as 0 mg brexpiprazole augmentation. We excluded quasi-randomized trials and studies where sequence generation was at high risk of bias, or allocation was clearly not concealed.

Types of participants

Patients were eligible if they were aged 18 years or older of both genders, with a primary diagnosis of MDD according to any of the standard operationalized diagnostic criteria (Feighner Criteria, Research Diagnostic Criteria, DSM-III, DSM-III-R, DSM-IV, DSM-5, ICD-10) with inadequate response to at least one trial of antidepressant.

Types of interventions

We compared brexpiprazole augmentation with the continuation of antidepressant treatment with placebo augmentation. We did not include active comparators, such as dose-escalation of the ongoing antidepressant, switching to another antidepressant, or adding another drug, because we were interested in the dose-effect relationship of brexpiprazole augmentation. We included treatment groups within and outside the licensed dose range as shown by the international drug approval agencies or guidelines.

Search methods for identification of studies

Electronic searches and research registers

We systematically searched Cochrane Central Register of Controlled Trials and PubMed from inception to 16 September 2021. We ran an additional search on PsycINFO from inception to 20 April, 2022. We used broad search terms for depression in conjunction with generic and commercial names of brexpiprazole (eAppendix2). We imposed no date, language or publication status restriction. No search filter was used. We searched ClinicalTrials.gov and the WHO's trials portal (ICTRP) from inception to 16 September 2021 to identify unpublished or ongoing studies.

Drug approval agencies

We searched the following drug approval agencies for additional published and unpublished data until 16 September 2021: Food and Drug Administration (USA), European Medicines Agency (EU), Medicines and Healthcare products Regulatory Agency (UK), Therapeutic Goods Administration (Australia) and Pharmaceuticals and Medical Devices Agency (Japan).

Reference lists and others

We checked the reference of all the included papers and review articles for additional references. We searched the website of Otsuka Pharmaceutical Co., Ltd. (Tokyo, Japan), which developed and is marketing brexpiprazole, contacted

the company and requested supplemental unpublished information about their pre-marketing and post-marketing trials. We also contacted experts in the field to identify unpublished and on-going trials.

Data collection and extraction

Two review authors (S.Og., S.Ob) independently screened and selected the included studies. Two review authors (S.Og., S.Ob) extracted data independently from the included studies. We used the Cochrane risk of bias tool Version 2 [27] to assess and summarize the risk of bias. Disagreements were resolved through discussion with a third member of the review team (Y.F.). Interrater agreements were excellent (96.7% agreement, intraclass correlation coefficient > 0.9 for the primary outcome; 94.4%, weighted kappa > 0.9 for risk of bias items).

Primary outcomes

Our primary outcome was efficacy (measured by the total number of responders, defined as 50% or greater reduction on a standardized observer-rating scale for depression). Our secondary outcomes were acceptability (measured by the total number of patients who dropped out for any reason), and tolerability (measured by the total number of patients who dropped out for adverse events). Those who had been randomized but not accounted for in the original study were assumed to have dropped out for some reason other than adverse events and without responding. We used the number of randomized patients as the denominator for all outcomes. We measured each outcome with odds ratios. [28,29]

Statistical analysis

We performed the analysis in *R* (Version 4.1.2 R foundation, Vienna, Austria)[30] using *dosresmeta* (Version 2.0.1) package[31] to conduct dose-effect meta-analysis and *meta* (Version 5.1-0) package[32] to synthesize the outcomes in placebo arms and to assess the publication bias.

Assessment of heterogeneity and reporting biases

We investigated the heterogeneity between studies by computing the variance partition coefficient, [33] which represents the percentage of variation that is attributed to heterogeneity rather than sampling error and can be interpreted similarly to the I^2. We decided not to draw funnel plots in accordance with the prespecified protocol, because we found fewer than 10 studies and funnel plots were likely to be poorly informative. [32]

Dose-effect meta-analysis

We performed a one-stage, random-effects, dose-effect meta-analysis [33]. We modelled the impact of doses on the odds ratios of the outcome (on log-scale) using the restricted cubic splines with three knots which offers a great flexibility with the least number of knots. Using more knots requires more dose-arm data to be reported to be able to reliably estimate the additional parameters. The same approach was also followed by previous dose-effect meta-analyses of antidepressants for MDD[16] and aripiprazole augmentation for antidepressant-refractory depression.[34]. In the primary analysis, we located the knots at 1mg, 2mg, and 3mg. We used the dose-effect curve of the primary analysis to estimate the 50% effective dose (ED50) and 95% effective dose (ED95), as it is customary in dose-effect analyses. ED50 and ED95 indicate the mean dose that produces 50% and 95%, respectively, of the maximum effect compared with placebo augmentation, expressed in log-odds ratio.

Sensitivity analyses

To ascertain the robustness of the primary analyses, we conducted the following sensitivity analyses: 1) excluding trials with overall high risk of bias, 2) including flexible-dose arms using maximum target dose, or 3) using different locations of knots.

RESULTS

We identified 336 records via database and registries, and one record with reference search. We assessed 32 full-text records for eligibility, and included six studies (three published[35–37] and three unpublished[38–40]) for primary analyses with 1,671 participants. As one unpublished trial[39] did not measure efficacy outcome, we included five studies for the efficacy analysis. (Fig 1) The lists of included and excluded studies are provided in the appendix (eAppendix4, eAppendix5). Table 1 presents the characteristics of the included studies.

The included studies were homogeneous by design, as all were double-blind, placebo-controlled, parallel-group, individually randomized, multi-center trials using very similar inclusion and exclusion criteria. All trials took place in north America or Europe and in outpatient settings. The first trial was registered in 2008.[38] In total, 920 participants were randomly assigned to an active drug and 751 were randomly assigned to placebo. Baseline age was similar among all studies except one[39] that recruited only elderly patients. The mean age was 44.8 years (standardized deviation [SD] 12.0); 1165 (69.7%) of 1671 reported were women. All studies defined depression according to the DSM-IV-TR diagnostic criteria. Baseline severity was similar among all studies and the mean reported baseline severity score on MADRS was 26.6 (SD 5.6). The duration of the acute treatment in all trials was 6 weeks. Pharmaceutical companies funded all the studies. All studies excluded patients with serious mental comorbidities, such as schizophrenia, bipolar depression, and alcohol or substance misuse. MDD patients with psychotic symptoms or presenting with suicidal ideation or behaviour were also excluded. All studies excluded participants who had electro-convulsive therapy during the current depressive episode. Antidepressant-refractory depression was defined as an inadequate response to 1-3 antidepressant trials of at least 6-12 weeks' duration during the current episode. Most of the continued antidepressants were either selective serotonin reuptake inhibitor or serotonin noradrenaline reuptake inhibitors. Dosing schedule for 1mg or more involved titration phase: 0.5mg/day in the first week, 1mg/day in the second week followed by continuation of 1mg/day or dose-escalation to 2 or 3mg/day. Five studies out of six were rated at overall low risk of bias, while one study[40] terminated early because of ineffective recruitment and was therefore rated at overall high risk of bias due to missing outcome data. (eAppendix6 eFigure1)

Assessment of heterogeneity and reporting biases

We assessed heterogeneity in the efficacy outcome (five studies). The values of variance partition coefficient were constantly low (<0.1) over the observed dose range (eAppendix7, eFigure2), which was not suggestive of significant heterogeneity. However, these assessments need to be carefully interpreted due to the small number of studies included.

Dose-effect meta-analysis

We present the estimated summary dose-effect curves in Fig 2 and the tabulation of results in Table 2. The dose-efficacy curve showed an increase up to doses around 2 mg, and then a flat to decreasing trend through the higher licensed dose up to 3 mg. ED50 was 0.88 mg (odds ratio [OR] 1.24, 95% confidence interval [CI] 1.04-1.46) and ED95 was 1.79 mg (OR 1.49, 95%CI 1.10-2.02). The shape of the dose-tolerability curve was comparable to that of the efficacy. The dose-

acceptability curve showed a monotonic increasing trend. Both had wide CI bands. Sensitivity analyses excluding trials with overall high risk of bias, including flexible dose arms using maximum target dose (for efficacy: 8 trials, 12 active treatment arms, 3 555 participants) generally confirmed the primary analyses (eAppendix9, eFigure5). Sensitivity analyses using different locations of knots confirmed that additional benefit is unlikely beyond 2mg and ED95 is likely to lie between 1 and 2mg. (eAppendix9.2, eFigure5) Post-hoc analyses of depressive symptoms using continuous outcomes (Montgomery Åsberg Depression Rating Scale and Hamilton Depression Rating Scale) and social functions (Sheehan Disability Scale) were in line with the primary analyses. The incidence of akathisia and restlessness showed a monotonic increasing trend, whereas the incidence of weight gain peaked off around 2mg and the dose-effect curve of insomnia was almost flat (post-hoc). (eAppendix10, eFigure6) According to the GRADE framework, the certainty of evidence for dose-effect relationship was moderate for efficacy (due to some concerns in imprecision), low for tolerability (due to serious concern in imprecision), and moderate for acceptability (due to some concerns in imprecision) (eAppendix12). Given an average response rate of 18% in the placebo augmented arms at 6 weeks (5 arms, 746 participants), the rate of dropout for adverse events of 1% (6 arms, 751 participants), and the rate of dropout for any reason of 12% (6 arms, 751 participants), brexpiprazole augmentation with the maximum target dose of 1.79mg (ED95) would translate into a response rate of 25% (95%CI: 20 to 31%), a rate of dropouts due to adverse events of 1% (95%CI: 0 to 4%), and a rate of dropout for any reason of 14% (95% CI: 10 to 20%).

DISCUSSION

To our knowledge, this is the first systematic review and dose-effect meta-analysis investigating brexpiprazole as an augmentation strategy for antidepressant-refractory depression. Our results show that brexpiprazole augmentation may achieve most of its efficacy at around 1-2 mg in the acute treatment of major depression with inadequate response to an initial antidepressant therapy, and that further additional benefits may be unlikely beyond 2 mg. This is in line with a positron emission tomography study, which found that multiple doses of 2 mg/day are expected to result in D2/D3 receptor occupancies of around 80%, which is said to be a clinically effective threshold. [41] Combined with pharmacodynamic and pharmacokinetic findings, dose-effect meta-analysis may contribute to the physiological studies of MDD. Our finding supports the currently recommended dose of brexpiprazole for augmentation therapy for MDD, but not the maximum dose. [23] This is also in line with the findings from a previous meta-analysis using an arbitrary categorization of doses (>2 mg vs ≤2 mg)[24], indicating that 2mg or a lower dose seemed to have better efficacy and lower incident of akathisia compared to higher doses. The maximum target dose currently recommended in the United States (3mg)[23] may be therefore potentially harmful and cost-ineffective for most of the patients, as it may prompt clinicians to prescribe too high a dose that only increases the risk of side effects without additional benefits. There is an ongoing three-arm trial that directly compares 1mg and 2mg brexpiprazole to placebo,[42] which may tell us whether 1mg or 2mg is more desirable. Our finding is in contrast with the previous network meta-analysis of antipsychotic augmentations for MDD that found low-dose atypical antipsychotics were not effective, [43] but in line with our dose-effect meta-analyses of aripiprazole augmentation for antidepressant-refractory depression that low-dose aripiprazole (2-5mg) may achieve most of its efficacy. [34] The discrepancy may be due to the arbitrary categorization of doses (low vs standard dose) and the relatively fewer number of trials included in the low-dose range in the network meta-analysis. It should be noted that even with brexpiprazole augmentation, about three quarters of antidepressant refractory depression patients do not respond in six weeks. To the best of our knowledge, comparative efficacy, tolerability and acceptability of

next-step treatments for those who failed to respond to antipsychotic augmentation have not been examined in randomized controlled trials. For the time being, clinicians may to apply 'trial-and-change' algorithm, in which evidence-based treatments, such as combining different classes of antidepressants [18], pharmacological augmentation with various non-antidepressant agents [19], psychotherapies [11] and neuromodulations [12], are subsequently applied.

Limitations

Our study has several limitations. First, the number of studies was small, leaving confidence intervals for tolerability and acceptability wide. Second, original studies excluded patients with other serious psychiatric comorbidities or MDD patients with psychotic symptoms. It is therefore unknown whether the result of this study can be generalized to those patient groups. This analysis does not refute the possibility that doses beyond 2mg might be still useful for MDD patients with psychotic symptoms. Third, we could not evaluate the impact of possible effect modifiers on the dose-effect relationship. While this study suggests 1 to 2 mg of brexpiprazole may offer most of its efficacy on average, it does not deny the possibility that a lower or higher dose might offer a better therapeutic effect to certain subgroups. Forth, the duration of the included studies was mostly limited to the acute phase treatment. A trial with 24-week follow-up period[44] found no additional benefit and more adverse events with brexpiprazole augmentation and we therefore remain cautious about its long-term use. An ongoing long-term trial[45] may provide additional insights.

Strengths

The strengths of the current study may be as follows. First, we treated dose as a continuous variable, thus avoiding arbitrary categorization of doses which could lead to spurious dose-effect relationships. Second, we examined dose dependency not only for efficacy but also for tolerability and acceptability. This enabled us to investigate not only the dose range that maximize the efficacy, but also the dose range that optimize the balance of efficacy, tolerability and acceptability. Third, doses of all the included studies were prospectively fixed and therefore can be used for investigating sal relationship. Flexible dose arms were included for sensitivity analyses and confirmed the primary analysis

Future research

The two ongoing trials[42,45] will add more insight to the dose-effect relationships of brexpiprazole augmentation and its long-term consequences. Future trials should consider comparing brexpiprazole augmentation head-to-head to other next-step treatment options, such as other antipsychotic augmentations. [46] Comparative efficacy of next-step treatments for those who failed to respond to antipsychotic augmentation should also be examined in randomized controlled trials.

CONCLUSION

Augmentation with brexpiprazole in the acute treatment of antidepressant-refractory depression may achieve most of its efficacy within 1 to 2 mg, whilst additional benefits may be unlikely beyond 2 mg. The drop-outs due to adverse events may not increase further beyond 2mg, but the overall drop-out rate seems to increase at greater dosages. Thus, 1-2mg

brexpiprazole may achieve an optimal balance between efficacy, tolerability and acceptability as acute augmentation treatment of antidepressant-refractory depression.

FIGURE LEGENDS

Fig 1 PRISMA2020 flow diagram

Fig 2 Dose-effect relationships of brexpiprazole augmentation

2a Response

2b Dropout for adverse events

2c Dropout for any reason

ED50=50% effective dose. ED95=95% effective dose. OR=odds ratio. The dotted lines represent 95% confidence intervals

Supporting information

1. Appendix.docx

Appendix (1. Protocol; 2. Search strings used for Cochrane Central Register of Controlled Trials and PubMed; 3. Amendments from the protocol; 4. List of all included studies; 5. List of excluded studies; 6. The revised Cochrane risk of bias tool summary (eFigure1); 7. Variance partition coefficient for efficacy (eFigure2); 8. Forest plot and dose-effect curve with box plots of each study (eFigure3, 4); 9. Sensitivity analyses (eFigure5); 10. Additional analyses (eFigure6); 11. Cumulative analysis (eFigure7); 12. GRADE evidence profile table))

2. PRISMA_2020.docx

PRISMA 2020 checklist

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DISCLOSURE STATEMENT

Conflict of interest disclosure:

YF has received consultancy fee from Panasonic outside the submitted work.

SOg declares no conflicts of interest.

SOb declares no conflicts of interest.

TH declares no conflicts of interest.

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Registration: PROSPERO (CRD42021273374).

Data availability statement: Data and code used for analyses are available from the corresponding author upon reasonable request.

Disclaimer: The views expressed are those of the authors and not necessarily those of the UK National Health Service, the NIHR, the UK Department of Health, or other affiliated organizations.

AUTHOR CONTRIBUTIONS

Y.F. contributed to the conceptualization, methodology, project administration, formal analysis, investigation, data curation, writing-original draft, writing-review & editing, visualization. S.Og. contributed to methodology, data curation, writing-review & editing. S.Ob. contributed to methodology, data curation, writing-review & editing. T.H. contributed to the methodology, software, validation, formal analysis, writing review and editing. E.G.O. contributed to the conceptualisation, methodology, validation, investigation, data curation, writing review and editing, supervision. K.K. contributed to conceptualization, project administration, writing-review & editing, supervision. Y.F., S.Og. and S.Ob had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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TABLES

Table 1 Characteristics of included studies

Study	Age, y, mean (SD)	No. of female	Baseline severity, MADRS, mean (SD)	No. of previous episodes, mean (SD)	Duration of current episode, mo, mean (SD)	Continued ADT	Augmentation	No. of participants	No. of responders	No. of dropouts due to AE	No. of dropouts for any reason
Thase et al,	45.2 (11.3)	137	27.1 (5.6)	3.8 (2.9)	13.7 (17.1)	Esci; Fluo; Paro	Placebo	191	28	0	13
2015a	44.1 (11.6)	130	26.6 (5.8)	3.8 (3.2)	13.5 (14.2)	CR; Sert; Dulo; Venl	BRE 2mg	188	41	6	13
Thase et al,	46.6 (11.0)	146	26.3 (5.3)	3.7 (4.9)	16.9 (35.0)	Esci; Dulo; Venl	Placebo	221	29	3	13
2015b	45.7 (11.6)	158	26.7 (5.6)	3.6 (3.9)	18.7 (43.0)	XR; Sert; Paro	BRE 1mg	226	49	3	10
	44.5 (11.2)	156	26.4 (5.2)	3.5 (2.8)	17.4 (33.0)	CR; Fluo	BRE 3mg	230	49	4	20
[illegible]bart et al,	42.7 (12.5)	144	26.2 (6.2)	3.2 (2.4)	19.2 (46.8)	Esci; Fluo: Paro;	Placebo	202	66	1	6
2018	43.0 (12.7)	147	27.1 (5.7)	3.1 (1.8)	13.3 (14.2)	Sert; Dulo; Venl	BRE 2mg	192	72	4	15
NCT00797966,	43.3 (11.5)	82	NA	NA	NA	Esci; Fluo; Paro	Placebo	126	25	1	16
unpublished	43.9 (10.8)	41	NA	NA	NA	CR; Sert; Desv; Venl XR	BRE 0.15mg	62	17	2	11
NCT01670279,	72.6 (1.5)	4	NA	NA	NA	Commercially	Placebo	5	NA	0	1
unpublished	74.7 (4.8)	9	NA	NA	NA	available antidepressant	BRE 3mg	13	NA	1	2
NCT01837797,	NA	3	NA	NA	NA	Commercially	Placebo	6	0	0	5
unpublished	NA	2	NA	NA	NA	available	BRE 1mg	3	0	0	2
	NA	6	NA	NA	NA	antidepressant	BRE 3mg	6	0	1	5

ADT=antidepressant drug therapy. AE=adverse events. BRE=brexpiprazole. Desv=desvenlafaxine. Dulo=duloxetine. Esci=escitalopram. Fluo=fluoxetine. Fluv=fluvoxamine. IQR=interquartile range. MADRS=Montgomery-Åsberg Depression Rating Scale. Miln=milnacipran. Paro=paroxetine. SD=standardised deviation. Sert=sertraline. Venl=venlafaxine.

Table 2. Effect of brexpiprazole augmentation at 1mg, 2mg and 3mg.

Outcome		Brexpiprazole							
		0 mg	(reference)	1mg		2mg		3mg	
Response	OR	1.00	(reference)	1.27	[1.05-1.54]	1.52	[1.12-2.06]	1.40	[0.95-2.08]
	Rate	18%	(5 arms)	22%	[19-26%]	25%	[20-32%]	24%	[17-32%]
Dropout for adverse events	OR	1.00	(reference)	1.72	[0.60-4.92]	2.48	[0.47-13.1]	1.77	[0.46-6.77]
	Rate	1%	(6 arms)	1%	[0-3%]	2%	[0-8%]	1%	[0-4%]
Dropout for any reason	OR	1.00	(reference)	1.12	[0.77-1.63]	1.30	[0.72-2.35]	1.77	[0.98-3.19]
	Rate	12%	(6 arms)	13%	[9-18%]	15%	[9-24%]	19%	[12-30%]

OR=odds ratio. 95% confidence intervals within bracket

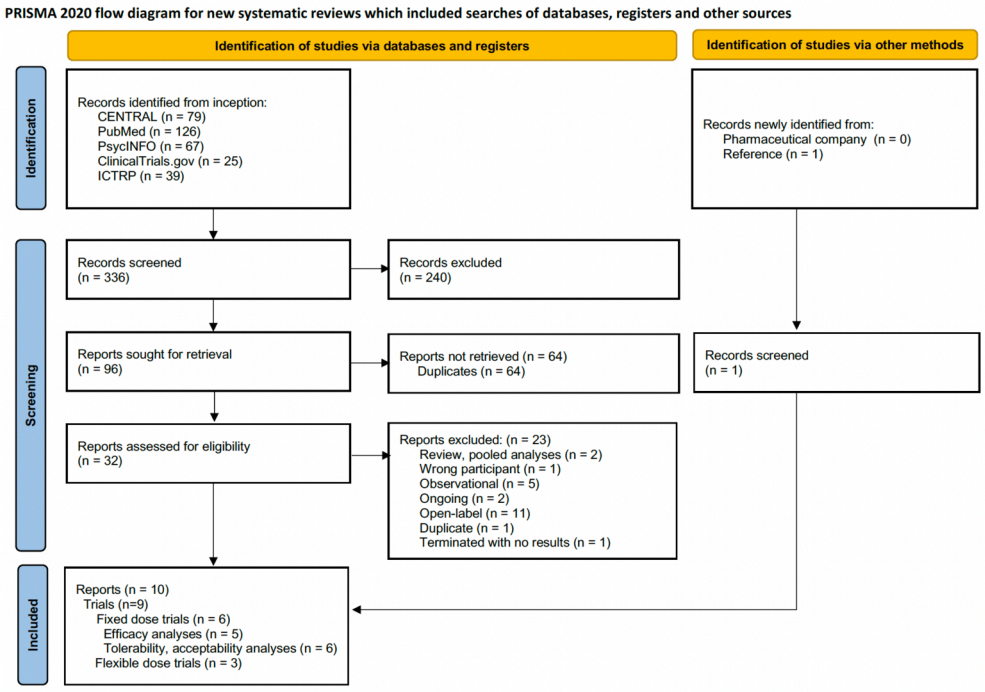

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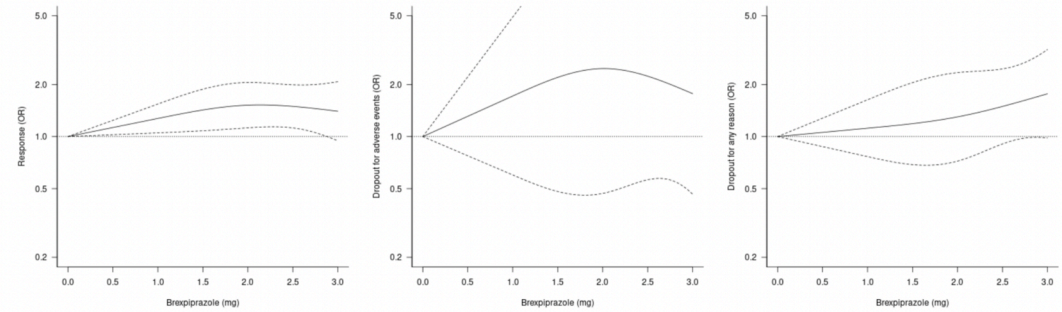
Fig 2 Dose-effect relationships of brexpiprazole augmentation

2a Response. 2b Dropout for adverse events. 2c Dropout for any reason



ED50=50% effective dose. ED95=95% effective dose. OR=odds ratio. The dotted lines represent 95% confidence intervals.

PCN_13438_R3Fig2.png