Indirect Meta-Analysis of Brexpiprazole Versus Aripiprazole in the Acute Treatment of Schizophrenia

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Abstract

Background: Brexpiprazole and aripiprazole are atypical antipsychotics that act as partial agonists at the dopamine D2 receptor. No head-to-head trial comparing brexpiprazole and aripiprazole in the treatment of schizophrenia is available. Here, we carry out a systematic review and comparison of the efficacy and safety of brexpiprazole and aripiprazole in schizophrenia treatment.

Methods: We employed an indirect meta-analysis to determine effect sizes from randomised placebo-controlled trials with brexpiprazole and aripiprazole in the acute treatment of schizophrenia. We compared responder rates, incidences of adverse events and serious adverse events, the number needed to treat (NNT) for response, number needed to harm (NNH) for adverse events or treatment discontinuation, and likelihood to be helped or harmed (LHH) as efficacy and safety indices of the two drugs.

Results: Five studies for each drug were included in the analysis. Similar risk differences vs. placebo were observed for responder rates under brexpiprazole (10.2%, $p = 0.0015$) and aripiprazole (10.3%, $p = 0.0003$). Higher incidences of adverse events and serious adverse events were seen under aripiprazole compared with brexpiprazole, however, the risk differences were not statistically significant. The NNT for response was 11 for both substances. For brexpiprazole compared with placebo, we did not find an increase of adverse events (NNH = 27, not significant), however, we found an increased number of adverse events for aripiprazole versus placebo (NNH = 17, $p < 0.05$). For both drugs, benefits were encountered more often than harms, with an LHH for any adverse event of 2.41 for brexpiprazole and 1.56 for aripiprazole, respectively.

Conclusions: The likelihood to be helped rather than harmed was greater with brexpiprazole compared to aripiprazole for the total rate of adverse events (ratio of brexpiprazole LHH/aripiprazole LHH = 1.54).

Background

Brexpiprazole is an atypical antipsychotic that acts as a partial agonist at the dopamine D2 receptor and was developed for the treatment of schizophrenia and as an adjunctive for major depressive disorder. Aripiprazole is an atypical antipsychotic primarily used for the treatment of schizophrenia and bipolar disorder. Here we intend to compare their clinical properties as reported in clinical trials.

Both drugs were used in one common clinical trial [1, 2], and in addition, the two drugs were used in an exploratory trial by Citrome and colleagues [3]. Here, we carried out a systematic review to evaluate the current evidence for treatment efficacy, safety and tolerability of brexpiprazole in schizophrenia in comparison to aripiprazole.

Both brexpiprazole and aripiprazole have been characterized as partial agonists at the dopamine D2 receptor [4, 5], which balance wanted and unwanted effects of D2 blockade. Brexpiprazole was specifically developed to enhance tolerability compared with existing treatments. For instance, it has a lower intrinsic activity at the dopamine D2 receptor [5] and its affinity to the serotonin receptors 5-HT_{1A} and 5-HT_{2A} is about ten times higher than the one of aripiprazole [4, 5]. These differences are thought to improve tolerability, especially with regard to akathisia [6–8].

The tolerability profile of an antipsychotic can be critical, because side effects may lead to treatment discontinuation [9, 10]. Adverse events related to extrapyramidal symptoms (EPS) or agitation were most strongly associated with non-adherence in a nationwide survey among schizophrenia patients [10], underscoring the importance of developing substances that avoid these.

We compare the efficacy and tolerability of brexpiprazole and aripiprazole by using the complete spectrum of outcomes applied at least once in the brexpiprazole as well as aripiprazole studies. These are: the number of completers; the Positive and Negative Syndrome Scale (PANSS) including the Positive subscale, the Negative subscale, the General Psychopathology subscale, and the PANSS Total score; the Clinical Global Impressions CGI-S and CGI-I; responder rates; incidences of adverse

events as documented in the respective study (AEs, TEAEs; OAEs); incidences of SAEs; discontinuations due to AE; and incidences of selected adverse events.

The effect sizes of active vs. placebo are quantified using number needed to treat (NNT), number needed to harm (NNH) and likelihood to be helped or harmed (LHH). NNT is an intuitive measure of the clinical impact that a treatment can have, making it a useful tool for treatment comparisons [11]. The interpretation of NNT is the number of patients to be treated with intervention A instead of intervention B to yield one additional positive outcome. In order to be useful, it is important to carefully define the outcome of interest before applying the concept of NNT [11].

In the case of unwanted effects, the equivalent measure is NNH. It gives the number of patients to be treated with intervention A instead of intervention B to yield one additional unwanted outcome.

Both numbers can be related using LHH to illustrate the trade-off between benefits and harms. LHH is calculated by dividing the NNH by the NNT and can thus be interpreted as a benefit-risk ratio. In order for an intervention to cause more benefit than harm, the LHH should be greater than 1.

The dopamine D2 partial agonists aripiprazole, brexpiprazole, and cariprazine have already been compared with respect to NNT, NNH and LHH by Citrome [12] using the then available short-term data. Here, however, we present an up-to-date comparison using all available evidence from randomised controlled trials selected by systematic database search.

Methods

The review protocol was not registered.

Eligibility criteria

Randomized controlled trials of brexpiprazole and/or aripiprazole p.o. in patients with current diagnosis of acute exacerbation of schizophrenia aged ≥ 18 years were eligible for this review. The study duration was restricted to 4 or 6 weeks because a maintenance treatment for relapse prevention over 26 weeks or longer was reported in only one trial for each drug.

Information sources

The following databases with DIMDI search interface (no longer available today) were used to identify eligible brexpiprazole studies: CCTR93 (Cochrane Central Register of Controlled Trials), ME60 (Medline), and EM74 and EA08 (Embase and Embase Alert). The DIMDI search was completed by searches in public clinical trials registries and databases: WHO ICTRP (International Clinical Trials Registry Platform), ClinicalTrials.gov, Pharmnet.Bund, EU Clinical Trials Register, LIVIVO, and Pubmed. One additional study [13] was provided by Lundbeck outside the searches shortly after publication in July 2018. The following databases were used to identify eligible aripiprazole studies: LIVIVO and Pubmed. This was completed by a search in the registry ClinicalTrials.gov.

Search

The basic strategy to identify brexpiprazole studies in databases with DIMDI search interface is shown in Additional file 1. The search was performed by Lundbeck on 02 May 2015 and completed by searches in ICTRP, ClinicalTrials.gov, Pharmnet.Bund, and EU Clinical Trials Register on the same day. Later updates in ClinicalTrials.gov, LIVIVO, and Pubmed were performed by the CRO in April and May 2018.

Study selection

Five brexpiprazole and five aripiprazole studies were suited for the 4 or 6 weeks treatment of patients with an acute exacerbation of schizophrenia. The studies were accepted with one placebo arm and one to three active treatment arms.

Data collection process

Data were extracted from brexpiprazole and aripiprazole full publications and study results in ClinicalTrials.gov, in one case supplemented by data from a poster presentation [1]. Data were entered directly into SAS files by a member of the statistics department of the CRO, printouts of which were checked against the original sources by an independent person from data management. Any corrections were quality controlled by means of printouts of the corrected files.

Data items

- *P: patient population*

The population of interest consists of adult patients (18 years or older) having a DSM-IV-TR diagnosis of schizophrenia confirmed by the Mini International Neuropsychiatric Interview (MINI) for Schizophrenia and Psychotic Disorders Studies. For studies which started before DSM-IV-TR was available an equivalent diagnosis can be sufficient.

- *I: intervention*

In the group of potentially eligible trials, the following doses were administered: brexpiprazole 0.25, 1, 2, 2.5, 2 – 4, 4, 5 mg/day, aripiprazole 2, 5, 10, 15, 20 mg/day. However, the doses of 0.25 and 5 mg brexpiprazole as well as 2 and 5 mg aripiprazole were not considered in the review because 0.25 mg brexpiprazole is, though approved by the European Medicines Agency for patients taking strong metabolic inhibitors, not approved in Switzerland and is not a recommended dose, 5 mg brexpiprazole and 2 mg aripiprazole are not approved, and 5 mg aripiprazole is predominantly used in the elderly who were not included in the studies considered in this paper. Results are reported in the pool of all approved and recommended doses.

- *C: comparator group*

Placebo was the only comparator eligible for the meta-analysis.

- *O: outcome measures*

In patients with acute schizophrenia the continuous outcome measures of this trial (PANSS, CGI) were commonly transformed into a responder criterion as follows:

- *If CGI is not available:* A response is defined as reduction from baseline in the PANSS Total score of $\geq 30\%$.
- *If CGI is available:* A response is defined as reduction from baseline in the PANSS Total score of $\geq 30\%$ and/or CGI-I = 1 (very much improved) or CGI-I = 2 (much improved).

Further binary outcomes are:

- the number of completers
- total rates of adverse events, defined by 'adverse events', 'treatment-emergent adverse events', or 'other adverse events than serious adverse events'
- rates of serious adverse events
- rates of study discontinuation due to adverse events
- incidences of selected adverse events.
- *S: items of study design*

The following items were used to characterise the study design: trial centres, concealment / blinding, allocation / randomisation, phases / duration of phases, experimental design, type of comparison, sample size determination.

Risk of bias in individual studies

The Cochrane risk of bias tool was used to describe the risk of bias in individual studies. This tool consists of five items: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and a catch-all item called 'other sources of bias'.

Summary measure

The report used Hedges's g , odds ratios, risk ratios, and risk differences to quantify the effect sizes of summary measures. However, we focussed on binary outcomes which allow a comparison of benefits and harm. Therefore, only two meta-analyses (responder rates, total incidences of adverse events) are shown as examples, further analyses are based on NNT and NNH (see below). *Synthesis of results*

Fixed effect and random effects models are used in the meta-analyses, however, the main results are based on NNT and NNH (see below).

Additional statistical analyses

Typical outcomes of placebo-controlled clinical trials are the absolute increase of responder rates (AIR) and the absolute risk reduction (ARR) of adverse events. The number needed to be treated with active drug instead of placebo for one additional patient to benefit is defined by $NNT = 1/AIR$, the number needed to be treated with active drug instead of placebo for one additional patient to be harmed by $NNH = 1/ARR$. Significance tests of NNT or NNH can be performed by confidence limits. If, e.g., ARR is calculated as $p_1 - p_0$ (p_1 = risk of active drug, p_0 = risk of placebo) with 95% confidence limits CI_{low} and CI_{upp} , then the lower limit $LL = 1/CI_{upp}$ and the upper limit $UL = 1/CI_{low}$ can be used as confidence limits of NNH. The confidence interval $CI_{low} \leq p \leq CI_{upp}$ consists of positive values if $CI_{low} > 0$ and negative values if $CI_{upp} < 0$. In these cases no problems occur with the interpretation of LL and UL. However, if zero is contained in the interval $p_1 - p_0$, the transformed interval of NNH consists of the intervals from

- $-\infty$ to $LL = 1/CI_{upp}$ (maximum value: -1)
- and $UL = 1/CI_{low}$ to $+\infty$ (minimum value: $+1$)

In this case we do not discuss the confidence limits but only use the relevant information that the difference between p_1 and p_0 is not significant if the confidence limits of NNH have different directions. If the confidence interval of NNH consists of only negative values (i.e. a significantly lower harm was observed with active drug compared with placebo), one should interpret the lower harm as benefit. The likelihood to be helped or harmed, defined by $LHH = NNH/NNT$, can then be used to quantify the value $-NNH$ as predictor of the responder rate. In general, the LHH describes how often benefits are encountered more frequently than harm.

Two methods are used to calculate confidence limits LL and UL: Wald and Wilson [11–18]. Wilson should be preferred in case of ARR values near 0 or 1 and small sample sizes, because the asymptotic method of Wald provides unreliable values in these situations.

Results

Study selection

The systematic literature review identified 177 records of potentially eligible trials on brexpiprazole after duplicate removal within search and 649 records of potentially eligible trials on aripiprazole without any procedure to remove duplicates within search. By means of title and/or abstract screening, 135 (brexpiprazole) and 541 (aripiprazole) records were classified as not

relevant. The remaining records were checked by means of full text screening (brexpiprazole: n = 42; aripiprazole: n = 28) or identified as reviews without additional information (aripiprazole: n = 80).

The full text screening led to the exclusion of 29 brexpiprazole and 20 aripiprazole records. The remaining records reported on 6 brexpiprazole and 6 aripiprazole trials (Figure 1, Figure 2). In both drug groups one trial dealt with the maintenance therapy in the state of stable disease after previous acute illness. Due to the small number of these trials, the maintenance therapy was not considered in the further analyses. The five relevant studies in each drug group are shown in Table 1.

Study characteristics

The trials in the acute treatment of schizophrenia included 3378 patients: brexpiprazole active drug n = 1525, brexpiprazole placebo n = 742, aripiprazole active drug n = 628, aripiprazole placebo n = 483. In all patients the age was ≥ 18 years and an acute exacerbation of schizophrenia was diagnosed. The daily doses of brexpiprazole were 1 mg: n = 324 (21.2%), 2 or 2.5 mg: n = 573 (37.6%), 2 – 4 mg flexible dose: n = 151 (9.9%), or 4 mg: n = 477 (31.3%). Aripiprazole was administered in daily doses of 10 mg: n = 352 (56.1%), 15 mg: n = 176 (28.0%), or 20 mg: n = 100 (15.9%). The duration of treatment lasted 4 or 6 weeks.

Risk of bias within studies

The methods of blinding and treatment allocation as well as the justification of anticipated effect size were often not specified. Furthermore, in three aripiprazole studies the variability of outcome data was repeatedly missing.

Synthesis of results

The synthesis of results is represented for responder rates, incidences of adverse events, and incidences of serious adverse events. Additional analyses are focused on NNT and NNH (see below).

Meta-analyses and indirect comparison of brexpiprazole and aripiprazole with respect to responder rates and total incidences of adverse events as well as serious adverse events

The meta-analysis of responder rates in the acute treatment of schizophrenia with a pool of approved and recommended doses of brexpiprazole and aripiprazole provided for both drugs significant superiority versus placebo of 10.2% (brexpiprazole: p = 0.0015) and 10.3% (aripiprazole: p = 0.0003), respectively (Figure 3a; Figure 4a). The indirect comparison of brexpiprazole vs. aripiprazole resulted in the risk difference -0.1%, CI = [-8.6%|8.4%], p = 0.9802.

The meta-analysis of total incidences of adverse events in the acute treatment of schizophrenia with a pool of approved and recommended doses of brexpiprazole and aripiprazole provided for both drugs no statistically significant differences compared with placebo (Figure 3b, Figure 4b). The indirect comparison of brexpiprazole vs. aripiprazole resulted in the risk difference -3.4%, CI = [-11.5%|4.6%], p = 0.4046.

The meta-analysis of incidences of serious adverse events in the acute treatment of schizophrenia with a pool of approved and recommended doses of brexpiprazole and aripiprazole provided for both drugs no statistically significant differences compared with placebo (Figure 3c, Figure 4c). The indirect comparison of brexpiprazole vs. aripiprazole resulted in the risk difference -1.9%, CI = [-4.9%|1.1%], p = 0.2080.

In the meta-analyses, I^2 was used as estimator of heterogeneity.

Absolute increase of the responder rates and number needed to treat (AIR, NNT)

The absolute increase of the responder rates (AIR) was 0.093 in both active drug study groups compared with placebo. This corresponds to NNT = 11 for both brexpiprazole and aripiprazole.

Both confidence intervals according to Wald as well as Wilson demonstrated significant effect sizes upon brexpiprazole and aripiprazole (Table 2).

Absolute risk reduction and number needed to harm (ARR, NNH)

In the brexpiprazole studies, no significant differences were observed between active drug and placebo in the rates of adverse events because the confidence intervals were compatible with higher adverse event rates upon active drug as well as lower adverse event rates upon active drug as compared with placebo (Table 3). Negative values of the absolute risk reduction (ARR) or the number needed to be treated for one additional patient to be harmed (NNH) indicate a lower adverse event rate upon active drug compared with placebo.

In the aripiprazole studies, the positive values of both LL and UL (LL: lower confidence limit; UL: upper confidence limit) indicate a significant increase of the adverse event risk upon aripiprazole compared with placebo in these studies (Table 3).

Rates of discontinuation due to adverse events (ARR, NNH)

In the case of brexpiprazole studies, the rate of discontinuation due to adverse events was significantly lower with active drug compared with placebo. In the aripiprazole studies, comparable rates of discontinuation due to adverse events were observed with active drug and placebo (Table 4).

Incidences of selected adverse events (ARR, NNH)

Caused by different directions of the effects, adverse events could appear as 'risks' or 'benefits' upon active drug as compared with placebo (Table 5). Risks were:

- akathisia upon both drugs, however, significant only with aripiprazole
- constipation only upon aripiprazole, but not significant
- diarrhoea only upon brexpiprazole, but not significant
- headache only upon aripiprazole and significant
- nausea upon both drugs, however, significant only with aripiprazole
- vomiting upon both drugs, but not significant
- weight increased upon both drugs, but not significant.

Benefits compared with placebo were:

- agitation upon both drugs, but not significant
- anxiety upon both drugs, but not significant
- constipation only upon brexpiprazole, but not significant
- diarrhoea only upon aripiprazole, but not significant
- dyspepsia upon both drugs, but not significant

- headache only upon brexpiprazole, but not significant
- insomnia upon both drugs, but not significant
- schizophrenia upon both drugs, however, significant only with brexpiprazole.

Likelihood to be helped or harmed (LHH) in the pool of doses in selected safety parameters with positive values of NNH

In safety parameters with positive values of NNH, the LHH describes how often benefits are encountered more frequently than harms. Using the NNT values from Table 2 (NNT brexpiprazole: 10.80; NNT aripiprazole: 10.71), the NNH values from Table 3 (rates of adverse events; brexpiprazole: 26.05; aripiprazole: 16.73), and selected NNH values from Table 5 (incidences of selected adverse events), the likelihood to be helped or harmed resulted in

- all adverse events : brexpiprazole 2.41 / aripiprazole 1.56 (ratio 1.54)
- akathisia : brexpiprazole 12.72 / aripiprazole 2.65 (ratio 4.80)
- nausea : brexpiprazole 6.21 / aripiprazole 1.18 (ratio 5.26)
- weight increased : brexpiprazole 2.66 / aripiprazole 3.29 (ratio 0.81).

Likelihood to be helped or harmed in the pool of doses (LHH) in selected safety parameters with negative values of NNH

The risk parameter schizophrenia provided negative values of NNH which were transferred to $-NNH$ and analysed as benefit measure 'NNT_S'. Using the NNT values from Table 2 (brexpiprazole: 10.80; aripiprazole: 10.71) and the NNT_S values from Table 5 as defined above, the likelihood ratio resulted in

- NNT_S/NNT : brexpiprazole 2.45 / aripiprazole 3.62 (ratio 0.676).

If the reduction of the adverse event schizophrenia with active drug versus placebo serves as predictor for the absolute increase of response, the higher accordance was observed under brexpiprazole compared with aripiprazole.

Discussion

Here, we present an indirect meta-analysis comparing the efficacy and safety of brexpiprazole with aripiprazole. We made indirect comparisons based on responder rates, incidences of adverse events, NNT, NNH, and LHH calculated based on data from all randomised controlled trials available to date. Previous analyses had included short-term studies mentioned in the respective product labeling [12].

NNT is a useful tool, showing effect sizes in an intuitive way as a proxy for the clinical relevance of efficacy results. In order to be meaningful, the outcome of interest must be carefully defined and should be important to the patient [11]. Here, it means the number of patients that need to be treated with brexpiprazole or aripiprazole instead of placebo for one additional patient to experience a 30% reduction in PANSS total score (or to achieve a CGI-I value of 1 or 2). A 30% PANSS reduction can be considered a clinically meaningful difference in real-world practice, reflected by CGI-I scores of at least 3 [19].

For unwanted outcomes, the equivalent measure is NNH. Again, it is important to first identify clinically meaningful negative outcomes before applying the concept of NNH [11]. Here, we calculated NNH for several negative outcomes of clinical interest. Correspondingly, our results are interpreted as the number of patients to be treated with brexpiprazole or aripiprazole

instead of placebo for one additional patient to a) experience any adverse event; b) discontinue treatment because of an adverse event or c) experience a specific adverse event common in schizophrenia treatment.

Both numbers can be related using the concept of LHH, the ratio of NNT and NNH. Here, we calculated LHH only for selected NNHs.

We used two different methods for calculating confidence limits by Wald and Wilson [14, 15] that both led to the same results regarding significance/non-significance, showing the robustness of the analysis.

The NNTs found here for brexpiprazole and aripiprazole were both 11, indicating comparable efficacy of both drugs. Usually, an NNT of 10 or lower is considered clinically relevant [11], however, this may vary depending on the indication of interest. The relatively high NNTs found here may also reflect high rates of placebo response in the trials that provided the data source. In general, increasing placebo responses are a problem in schizophrenia trials [20, 21]. In addition, the relatively high NNT for brexpiprazole could be caused by the inclusion of the subtherapeutic dose of 1 mg in this meta-analysis. Eventually, it is noted that regulatory authorities throughout the world have approved both brexpiprazole and aripiprazole for the treatment of schizophrenia showing that both drugs are efficacious for the treatment of this disease.

In his previous analysis, Citrome found smaller but comparable NNTs of 7 and 8 for brexpiprazole and aripiprazole, respectively [12]. In an exploratory, open label study, brexpiprazole showed a higher response rate (60.9%) than aripiprazole (48.5%), using the same response criteria that were used here [3]. Taken together, the available data indicate that the efficacy of brexpiprazole is at least comparable to that of aripiprazole.

The NNHs found in this study were mostly high and not significantly different from placebo. The number of patients needed to treat with brexpiprazole for any additional adverse event to occur was 27 and not significantly different from placebo, whereas for aripiprazole, it was 17 and significantly different from placebo. Considering individual adverse events, the NNHs found here are mostly in the high double-digit or triple-digit range, which are acceptable numbers for a good tolerability profile [11]. Only the NNHs for akathisia, headache and nausea upon aripiprazole treatment were significantly different from placebo. These data indicate better tolerability for brexpiprazole over aripiprazole.

In some instances, even negative NNHs were found, indicating a benefit rather than a harm for the active substance. This was the case for discontinuation because of adverse events upon brexpiprazole as well as several adverse events.

For some specific unwanted outcomes, we additionally calculated LHH. We found that brexpiprazole treatment was 2.4 times more likely to lead to a 30% PANSS reduction than any adverse event, compared with a likelihood of 1.6 for aripiprazole, also indicating better overall tolerability for brexpiprazole. The advantages for brexpiprazole were even more pronounced for akathisia and nausea, with a benefit/risk-ratio of 12.7 and 6.2, respectively. Only for weight gain, aripiprazole had a better LHH than brexpiprazole, but brexpiprazole was still 2.7 times more likely to reduce PANSS by 30% than to cause a weight gain of at least 7%. For the adverse event of schizophrenia, both drugs yielded a benefit compared with placebo. In this case, the LHH gives a measure of how well the avoidance of schizophrenia as an adverse event correlates to a treatment response. This correlation was stronger for brexpiprazole.

In his 2015 analysis, Citrome found comparable NNH and LHH values [12]. However, these were based on fewer data, namely only studies from the product labelling.

In a separate analysis, Citrome focused on sedating and activating adverse events as they were reported in the product labelling of several antipsychotics. These types of events require special attention because they may be especially strongly associated with nonadherence [10]. In Citrome's analysis, brexpiprazole was one of only two antipsychotics out of 11 classified as neither activating or sedating [22]. This is in line with our results, indicating an advantage for brexpiprazole especially when considering akathisia.

In an exploratory, open-label trial with brexpiprazole and aripiprazole, a lower incidence of akathisia was found in the brexpiprazole group (9.4% vs. 21.2%) [3], which is in line with our results. Both drugs elicited similar overall rates of adverse events in this trial (57.8% vs. 63.6%).

The present meta-analysis indirectly compares brexpiprazole and aripiprazole using data from randomised clinical trials.

Here, we analysed data from short-term trials of maximally 6 weeks, and our finding should ideally be confirmed using data from long-term treatment, where treatment outcome may be defined differently (e.g. avoiding relapse) and some adverse events may resolve over time.

If possible, the results found here should be confirmed by a randomised head-to-head trial of brexpiprazole and aripiprazole.

Conclusions

We used all published randomised, placebo-controlled short-term clinical trials studying brexpiprazole and aripiprazole to establish an indirect comparison using responder rates, incidences of adverse events, NNT, NNH, and LHH. We found that brexpiprazole and aripiprazole show comparable efficacy, while brexpiprazole shows advantages in terms of tolerability.

Abbreviations

AIR Absolute increase of responder rate

ARR Absolute risk reduction

CGI-I Clinical global impression - improvement

CI Confidence interval

CRO Contract research organisation

EPS Extrapyramidal symptoms

LHH Likelihood to be helped or harmed

LL Lower limit

NNH Number needed to harm

NNT Number needed to treat

PANSS Positive and negative syndrome scale

UL Upper limit

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests [A1]

bitte ausfüllen!

ES..., MF is an employee of Lundbeck GmbH, the statistical evaluation was performed by JS (IAS)

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Authors' contributions

ES, MF and JS designed research. MF and JS performed literature searches. JS performed statistical analyses. ES, MF and JS wrote the paper.

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[A1]bitte ausfüllen

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Tables

Table 1: Relevant trials with brexpiprazole and aripiprazole in the acute treatment of schizophrenia

Brexpiprazole	Aripiprazole
BREX1: 331-10-231 (VECTOR), Correll et al. 2015	ARI1: RVP-20-001 (REFRESH), Cantillon et al. 2017
BREX2: 331-10-002 (JAPIC), Ishigooka et al. 2018	ARI2: Cutler et al. 2006
BREX3: 331-10-230 (BEACON), Kane et al. 2015	ARI3: RGH-MD-04, Durgam et al. 2015
BREX4: LU14644A (EudraCT 2012-002252-17)	ARI4: McEvoy et al. 2007
BREX5: 331-07-203 (STEP 203), McQuade et al. 2011	ARI5: 331-07-203 (STEP 203), McQuade et al. 2011

Table 2: Responder rates of active drug and placebo: Number needed to treat (NNT) with confidence limits (LL, UL)

Drug	Response		AIR	NNT	Wald confidence limits			Wilson confidence limits		
	Active drug	Placebo			LL	UL	Sign.	LL	UL	Sign.
BREX	0.413	0.320	0.093	10.80	7.43	19.83	X	7.46	20.05	X
ARI	0.390	0.296	0.093	10.71	6.68	26.93	X	6.72	27.35	X

BREX = brexpiprazole; ARI = aripiprazole; AIR = absolute increase of the responder rate; LL = lower 95% confidence limit; UL = upper 95% confidence limit; Sign. = significance; X = $p < 0.05$

Table 3: Rates of adverse events with active drug and placebo: Number needed to be treated for one additional patient to be harmed (NNH) with confidence limits (LL, UL)

Drug	Adverse events		ARR	NNH	Wald confidence limits			Wilson confidence limits		
	Active drug	Placebo			LL	UL	Sign.	LL	UL	Sign.
BREX	0.563	0.524	0.038	26.05	12.17	-185.73	ns	12.19	-189.49	ns
ARI	0.662	0.602	0.060	16.73	8.53	421.50	X	8.55	395.66	X

BREX = brexpiprazole; ARI = aripiprazole; ARR = absolute risk reduction; LL = lower 95% confidence limit; UL = upper 95% confidence limit; Sign. = significance; X = $p < 0.05$; ns = not significant

Table 4: Rates of discontinuation due to adverse events with active drug and placebo: Number needed to be treated for one additional patient to be harmed (NNH) with confidence limits (LL, UL)

Drug	Discontinuation due to AE		ARR	NNH	Wald confidence limits			Wilson confidence limits		
	Active drug	Placebo			LL	UL	Sign.	LL	UL	Sign.
BREX	0.091	0.123	-0.031	-31.75	-261.64	-16.90	X	-206.19	-16.56	X
ARI	0.067	0.070	-0.004	-284.54	37.70	-29.81	ns	38.23	-28.66	ns

BREX = brexpiprazole; ARI = aripiprazole; ARR = absolute risk reduction; LL = lower 95% confidence limit; UL = upper 95% confidence limit; Sign. = significance; X = $p < 0.05$; ns = not significant

**Table 5: Incidences of selected adverse events in the pool of doses:
Number needed to be treated for one additional patient to be harmed (NNH) with confidence limits (LL, UL)**

Symptom	Drug	Incidence		ARR	NNH	Wald confidence limits			Wilson confidence limits		
		Active drug	Placebo			LL	UL	Sign.	LL	UL	Sign.
Agitation	BREX	0.074	0.087	– 0.013	– 76.85	48.28	– 21.39	ns	54.12	– 20.09	ns
	ARI	0.091	0.104	– 0.014	– 72.68	39.84	– 19.00	ns	40.98	– 18.47	ns
Akathisia	BREX	0.052	0.045	0.007	137.42	38.67	– 88.47	ns	40.10	– 78.17	ns
	ARI	0.069	0.034	0.035	28.41	15.22	213.23	X	15.26	533.44	X
Anxiety	BREX	0.073	0.105	– 0.033	– 30.64	25.10	– 9.51	ns	29.12	– 8.63	ns
	ARI	0.086	0.096	– 0.010	– 105.26	33.75	– 20.56	ns	34.86	– 19.77	ns
Constipation	BREX	0.056	0.081	– 0.025	– 40.15	59.66	– 15.02	ns	78.69	– 13.78	ns
	ARI	0.071	0.062	0.009	117.47	22.19	– 35.68	ns	22.72	– 32.21	ns
Diarrhoea	BREX	0.036	0.024	0.013	78.30	25.74	– 75.13	ns	27.22	– 48.91	ns
	ARI	0.040	0.045	– 0.005	– 193.81	40.37	– 28.50	ns	42.06	– 25.72	ns
Dyspepsia	BREX	0.040	0.047	– 0.006	– 160.35	44.16	– 28.48	ns	50.33	– 24.94	ns
	ARI	0.095	0.097	– 0.002	– 570.43	23.94	– 22.08	ns	24.77	– 20.88	ns
Headache	BREX	0.089	0.092	– 0.003	– 385.44	44.11	– 35.89	ns	46.17	– 34.31	ns
	ARI	0.173	0.129	0.044	22.77	11.61	586.51	X	11.69	146.20	X
Insomnia	BREX	0.113	0.114	– 0.001	– 857.91	33.80	– 31.33	ns	35.03	– 30.10	ns
	ARI	0.140	0.158	– 0.018	– 55.13	35.16	– 15.45	ns	36.11	– 15.20	ns
Nausea	BREX	0.045	0.030	0.015	67.02	27.24	– 145.66	ns	28.31	– 99.60	ns
	ARI	0.128	0.049	0.079	12.63	8.69	23.13	X	8.73	24.16	X
Schizo- phrenia	BREX	0.089	0.127	– 0.038	– 26.42	– 125.67	– 14.76	X	– 109.27	– 14.46	X
	ARI	0.053	0.078	– 0.026	– 38.76	33.72	– 12.31	ns	30.99	– 11.72	ns
Vomiting	BREX	0.054	0.047	0.006	157.49	24.42	– 35.40	ns	26.54	– 28.85	ns
	ARI	0.077	0.059	0.019	53.73	18.10	– 55.44	ns	18.40	– 47.79	ns

Weight increased	BREX	0.070	0.035	0.035	28.77	14.21	– 1163.80	ns	13.99	– 311.46	ns
	ARI	0.060	0.032	0.028	35.19	9.70	– 21.64	ns	7.54	– 24.38	ns

BREX = brexpiprazole; ARI = aripiprazole; ARR = absolute risk reduction; LL = lower 95% confidence limit; UL = upper 95% confidence limit; Sign. = Significance; X = $p < 0.05$; ns = not significant

Figures

Figure 1

Literature flow chart brexpiprazole

(a) Responder rates

(b) Total incidences of adverse events

(c) Incidences of serious adverse events

Figure 2

Literature flow chart aripiprazole

(a) Responder rates

(b) Total incidences of adverse events

(c) Incidences of serious adverse events

Figure 3

Meta-analysis of risk differences versus placebo under brexpiprazole and aripiprazole BREX1: 331-10-231 (VECTOR), Correll; BREX2: 331-10-002 (JAPIC), Ishigooka; BREX3: 331-10-230 (BEACON), Kane; BREX4: LU14644A (EudraCT 2012-002252-17); BREX5: 331-07-203 (STEP 203), McQuade; ARI1: RVP-20-001 (REFRESH), Cantillon; ARI2: Cutler; ARI3: RGH-MD-04, Durgam; ARI4: McEvoy; ARI5: 331-07-203 (STEP 203), McQuade (a) Responder rates (b) Total incidences of adverse events (c) Incidences of serious adverse events

Figure 4

Funnel plots of risk differences versus placebo under brexpiprazole and aripiprazole a) Responder rates b) Total incidences of adverse events c) Invidences of serious adverse events

Supplementary Files

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