Master thesis

Antihypertensive medications in antipsychotic treatments: A systematic review and network meta-analysis

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Preface

During the bachelor Pharmacy, I followed the course *Psychopharmacology* in which different psychiatric diseases were being treated, such as ADHD, sleeping disorder, depression, and schizophrenia. I found it very interesting to dive into the pathophysiology and treatment of these diseases, and from then on, I discovered that my interest lays in this field. My interest was further confirmed during a master's course, named *Individual Pharmacotherapy*. Here, depression, bipolar disorder, anxiety disorder, schizophrenia, and dementia were subjects of the course. The focus was to compose an individual pharmacotherapy for psychiatric patients, which was very complex. But since this topic is my genuine interest, I really enjoyed this challenge.

For my master thesis, I wanted to conduct research that was about psychopharmacology. I also decided to find a research project abroad to challenge myself and hoping to develop myself more as an individual. I was able to be assigned to a research project, which is entitled as *"Antihypertensive medications in antipsychotic treatment: A Systematic Review and Network Meta-analysis"*. For the past 5 months, I have performed this research at the Neuropharmacology and Pain research group at the University of Barcelona under supervision of Prof. Francisco Ciruela Alférez, Dr. Sebastià Videla, and Thiago Carnaval.

It was a blast to be part of the research group, and I really enjoyed being in an environment with PhD students which gave me more insight in the world of research. I loved the interaction with everyone in the laboratory, and I am very impressed by the passion they deliver in their own research. This has driven me to explore more in the field of experimental research.

More importantly, I enjoyed working with my supervisors. I would say that the teamwork was pleasant, open, and comfortable. For that, I am very thankful for my supervisors and for the support and guidance they have provided me during my research project.

Lastly, I am very happy that I have got the chance to contribute to research abroad and to make international relationships in the field of research. I am also glad that I devoted my time into research that will hopefully contribute to the treatment of psychosis.

Sincerely,

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Abstract

Background: It has been long postulated that the Renin-Angiotensin System (RAS) exists in the brain, and some evidences suggests an interaction between RAS and the dopaminergic system in the brain. This suggestion was also raised in the study of Martínez-Pinilla and colleagues (2015), whereby the formation of Angiotensin II Type 1 Receptor (AT_1R) and Dopamine 2 Receptor (D_2R) heteromer is ascertained. In addition, they have shown the ability of candesartan (AT_1R-inhibitor) to block D_2R-signaling. These findings indicate that drugs selective for AT_1R can alter the functional response of D_2Rs, which is interesting for diseases in which the dopamine signaling is disrupted. Since symptoms of psychosis are mediated by a hyperactivity of dopamine on D_2Rs in the mesolimbic pathway, we hypothesize that angiotensin agents (AAs) could have a potential beneficial effect in psychosis.

Methods: We conducted a systematic review and random effects network meta-analysis. Multiple databases (i.e., PubMed, Embase, and ClinicalTrials.gov) were searched from April 8th, 2022, to May 6th, 2022, to identify all randomized controlled trials (RCTs) investigating associations between the effect of AHM treatment and psychosis.

Results: Out of 6416 yielded publications, 5 RCTs were included with data on SNP and telmisartan for 162 participants with schizophrenia or schizoaffective disorder. The pooled mean difference compared with placebo on PANSS-G scale was -2.18 (95% CI: -3.91; -0.46), on PANSS-P scale it was -0.88 (95% CI: -1.66; -0.09), and on PANSS-N scale it was -2.06 (95% CI: -4.42; 0.31).

Discussion: This study suggests a potential beneficial effect of SNP and telmisartan on the positive symptoms of schizophrenia. However, since there were insufficient RCTs to create a robust network based on randomized data alone, the results should be interpreted as an indication. To further investigate the association between the effects of AHM and psychosis, new clinical trials are needed.

Keywords: psychosis, schizophrenia, schizoaffective disorder, antihypertensive medication, sodium nitroprusside, telmisartan, clinical trial, systematic review, network meta-analysis.

Samenvatting

Achtergrond: Het is al lang bekend dat er een Renine-Angiotensine-Systeem (RAS) in het brein bestaat en bovendien wordt er gesuggereerd dat er een mogelijke interactie bestaat tussen het RAS en het dopamine systeem in het brein. Deze suggestie komt overeen met de bevindingen uit de preklinische studie van Martínez-Pillina et al. (2015), waarin de formatie van Angiotensine II Type 1 Receptor (AT_1R) en Dopamine 2 Receptor (D_2R) heteromeer is vastgesteld in het striatum van een rat. Daarnaast is er geconstateerd dat candesartan (AT_1R-remmer) de D_2R signalering kan remmen. Deze bevindingen geven aan dat geneesmiddelen die selectief zijn voor AT_1Rs de D_2R signalering kunnen beïnvloeden wat belangwekkend is voor aandoeningen waarbij de dopamine signalering is verstoord. Aangezien de symptomen van psychose gemedieerd zijn door een hyperactiviteit van dopamine op de D_2Rs in het mesolimbische route, stellen wij de hypothese dat middelen waarvan de werking gerelateerd is aan angiotensine II (ARB's en ACE-remmers) een mogelijk voordelig effect kunnen bewerkstelligen in psychose.

Methodes: We hebben een systematische beoordeling en een netwerk meta-analyse uitgevoerd. Verschillende databanken, zoals PubMed; Embase en ClinicalTrials.gov, zijn geraadpleegd van 8 april 2022 tot 6 mei 2022 om alle gerandomiseerde klinische onderzoeken (RCT's) die het effect van verschillende antihypertensiva op psychose onderzochten te identificeren.

Resultaten: Van de 6416 verkregen publicaties zijn er 5 gerandomiseerde klinische onderzoeken geïncludeerd. Deze RCT's bevatte data over SNP en telmisartan voor 162 deelnemers met schizofrenie of schizo-affectieve stoornis. De *pooled mean difference* vergeleken met placebo voor de PANSS-G schaal was -2.18 (95% CI: -3.91; -0.46), voor de PANSS-P schaal was het -0.88 (95% CI: -1.66; -0.09) en voor de PANSS-N schaal was het -2.06 (95% CI: -4.42; 0.31).

Discussie: De resultaten suggereren een potentieel voordelig effect van SNP en telmisartan op de positieve symptomen van schizofrenie. Echter, aangezien er onvoldoende RCT's waren om een robuust netwerk te creëren gebaseerd op alleen gerandomiseerde gegevens, moeten de resultaten worden geïnterpreteerd als een indicatie. Om de relatie tussen het effect van antihypertensiva en psychose verder te kunnen bestuderen zijn er nieuwe klinische onderzoeken nodig.

Abbreviations

95% CI	95% Confidence Interval
AA	Angiotensin Agent
ACE	Angiotensin Converting Enzyme
AHM	Antihypertensive Medication
AT_1R	Angiotensin Type I Receptor
BB	Beta Blocker
BPRS-18	Brief Psychiatric Rating Scale
CANTAB	Cambridge Neuropsychological Test Automated Battery
CCB	Calcium Channel Blocker
CDRS	Calgary Depression Rating Scale
CGI	Clinical Global Impression
D_2R	Dopamine 2 Receptor
DB	Double Blind
MD	Mean Difference
NA	Not Assessed
PANSS	Positive and Negative Syndrome Scale
PANSS-G	Positive and Negative Syndrome General Psychopathology Scale
PANSS-N	Positive and Negative Syndrome Negative Scale
PANSS-P	Positive and Negative Syndrome Positive Scale
PANSS-T	Positive and Negative Syndrome Total score
PI	Prediction Interval
QLS	Quality of Life Scale
RAS	Renin-Angiotensin System
RCT	Randomized Controlled Trial
RD	Randomized
RoB	Risk of Bias
SPCD	Sequential Parallel Comparison Design
SANS	Scale for Assessment of Negative Symptoms
SD	Standard Deviation
SNP	Sodium Nitroprusside
SWM	Spatial Working Memory
TRS	Treatment Resistant Schizophrenia

Table of contents

1. Introduction

Psychosis is a condition, in which sever disruptions of the thought and emotions are present, resulting in a loss of contact with reality. This can be expressed in psychotic symptoms, such as delusions, hallucinations, disorganized thoughts, and disorganized behaviors. However, psychosis is not an independent disorder itself. It can be part of primary psychiatric disorders, in which psychosis defines the disorder, such as schizophrenia. Also, it can occur secondary under neurologic or medical conditions, like in Alzheimer's Disease [1,2]. The global prevalence of psychotic disorders is 4.6 per 1000 persons [3], and the incidence of all psychotic disorders is 26.6 per 100 000 person-years [4].

Several theories for the pathophysiology of psychosis have been speculated, whereby the dopamine hypothesis is the core theory. The dopamine hypothesis implies the excessive striatal dopaminergic signaling due to hyperactivity of dopamine at dopamine 2 receptors (D_2Rs) in the mesolimbic pathway [1,2]. Therefore, the mainstay of the treatment is aimed at blocking D_2Rs with antipsychotics, which counteracts the dopamine hyperactivity in the mesolimbic pathway. However, this mechanism of action is not restricted to the mesolimbic pathway, but it also affects other dopamine pathways in the brain. Consequently, adverse side effects are likely to occur while being treated with antipsychotics [2]. This contributes to a non-satisfactory antipsychotic treatment, and often, the treatment consists of treating the side effects rather than the original disease, leading to noncompliance. Next to this, most patients do not respond to the treatment, even though antipsychotics are effective in treating psychosis [5,6]. In fact, only 15-25% of the patients treated with antipsychotics achieve full symptom remission [7]. So, there is room for improvement in the treatment of psychosis.

The existence of a Renin-Angiotensin System (RAS) has been long postulated, and moreover, some evidences have suggested an interaction between RAS and the dopaminergic system in the brain [8,9]. In fact, Martínez-Pinilla and colleagues (2015) have ascertained the formation of angiotensin type I receptor (AT_1R) and D_2R heteromers in rat striatum. In addition, they have shown that candesartan, an AT_1R-antagonist, was able to block D_2R-signaling [8]. Besides angiotensin agents (AAs), other major antihypertensive drug classes have also been investigated in the field of neuropsychiatry. Colbourne et al. (2021) studied the relationship between antihypertensive medication (AHM) classes and psychiatric disorders. The AHM classes were Calcium Channel Blockers (CCBs), Beta Blockers (BBs), AT_1R blockers, Angiotensin Converting Enzyme (ACE) inhibitors, and diuretics. They have concluded that AHM classes are differentially associated with the incidence of psychiatric disorders, in which AT_1R-antagonists showed the most advantageous profile and BBs the least [10]. These findings support the potential role for angiotensin agents in psychiatric disorders.

Since the treatment of psychosis is far from optimal, it is reasonable to consider drug-repurposing for treatment optimization, and AAs and other AHMs could help to control psychotic symptoms. Our aim was to estimate the effect of antihypertensive medications, whereby angiotensin

agents were compared to non-angiotensin agents, on psychosis by conducting a systematic review and meta-analysis. We hypothesized that the use of AAs would be beneficial for patients with psychosis.

2. Material and methods

2.1. Search method

The PRISMA 2020 statement was used for the guidance of this study [11]. Searches in PubMed, Embase, and ClinicalTrials.gov were conducted to identify relevant publications. The search was restricted to a period window from 1 January 2000 to 6 May 2022, and the following keyword combinations were used: “psychiatry” OR “psychosis” OR “schizophrenia” AND “antihypertensives” AND “clinical trial”. The last search was conducted on 6 May 2022.

Since psychosis is not an independent disease itself, we decided to use other keywords that are related to psychosis to identify the utmost possible publications relevant to our subject. We choose to use “schizophrenia” as keyword because psychosis is a defined feature in schizophrenia. But there are more psychiatric disorders wherein psychosis occurs, and therefore we decided to use the keyword “psychiatry” to cover this.

2.2. Data selection

Two reviewers (M.B. and T.C.) assessed studies for eligibility by screening titles and abstracts independently. Studies were identified as potentially relevant if they met the following inclusion criteria: (1) randomized controlled trial, (2) psychosis or related disorder as condition, (3) clearly defined reduction of psychotic symptoms as outcome, and (4) antihypertensive medication treatment as exposure. Studies were identified as irrelevant if they met the following exclusion criteria: (1) participants < 18 years, (2) no full-text article, (3) case reports, letters, or book chapters, and (4) a lack of follow-up.

2.3. Data extraction

The full-text articles of potentially relevant studies were obtained and examined for inclusion in the analysis. One reviewer (M.B.) conducted data extraction, and this was verified by a second (T.C.) and a third reviewer (S.V.). Incongruities were debated between the reviewers until finding an outcome that all three agreed upon, and authors were approached to obtain study data when necessary.

The following data were extracted from each study:

- The country where the study took place;
- The study design;
- The condition of the participants;
- The treatment duration;

- The presence of a follow-up with details;
- The sample size per treatment arm;
- The name, dose, and route of administration of the intervention and comparison; and
- The psychiatric outcome measures.

2.4. Data analysis

Mean difference with 95% confidence interval (95% CI) was used to estimate the effect of AHMs on a common psychiatric outcome measure compared with placebo. For calculating mean differences and 95% CIs, Microsoft Excel was used. Easymeta was used to conduct a random-effects meta-analysis. A random-effects model was selected, since the included studies are random samples of a population. In Easymeta, a prediction interval (PI) was also calculated, as well as the heterogeneity using I^2. Also, sensitivity analyses were performed based on the study quality. See Appendix A for the quantitative analysis procedure.

2.5. Quality assessment

The risk of bias was assessed for all RCTs using the Cochrane Risk of Bias 2 tool [12]. This was done independently by three reviewers (M.B., T.C., and S.V.). Through discussion, a common assessment on the risk of bias was achieved.

3. Results

3.1. Study selection

The search recruited a total of 6416 publications that were screened by title and abstract, which yielded 7 potentially eligible studies that met the inclusion criteria. The full-text article of these studies was evaluated in detail, and eventually 5 RCTs were included for analysis [13–17]. See Figure 1 for the flowchart of the full search strategy and see Table 1 for the number of hits per search term and per database.

After full-text examination, two studies were excluded from the analysis. One study was a recruiting study at the time of data-extraction, whereas important study data could not be gathered [20]. The other study comprised of Treatment Resistant Schizophrenia (TRS) patients, while the study population of other studies were patients with schizophrenia or with schizoaffective disorder. The main difference between TRS and schizophrenia or schizoaffective disorder is the severity of the disease, in which TRS is more severe. Consequently, TRS-patients will likely have less of a response rate. For an equal comparison between studies, this study was excluded. In addition, the latter study also met one exclusion criteria, that is, the published article was a letter to the editor [18].

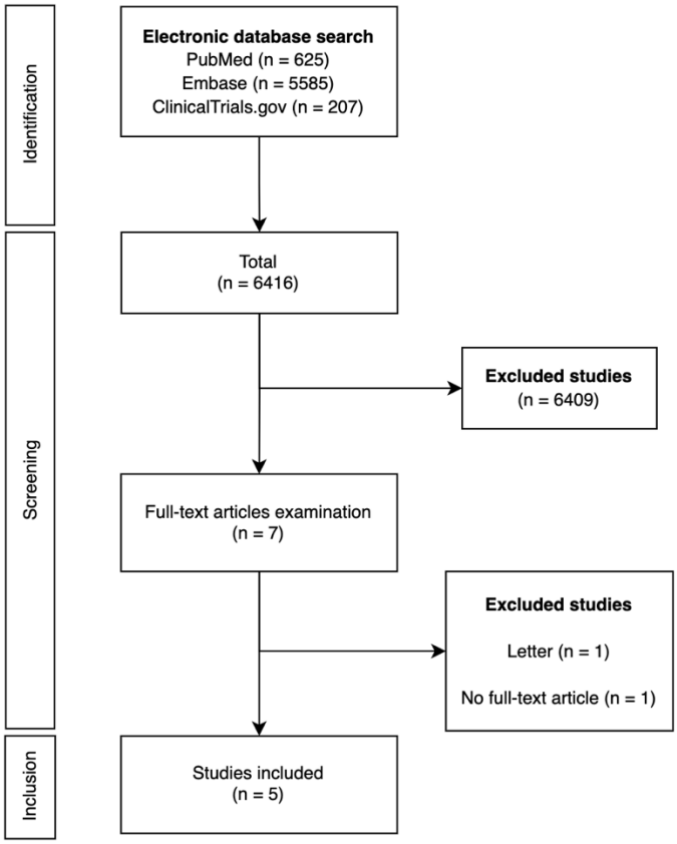

Figure 1. Flow diagram of the search strategy.

Table 1. Hits per search term and per database.

No.	Search terms	Hits Total	Hits per Database
1	Psychiatry AND antihypertensives AND clinical trial	3512	
	PubMed		544
	Embase		2916
	ClinicalTrials.gov		52
2	Psychosis AND antihypertensives AND clinical trial	1938	
	PubMed		24
	Embase		1770
	ClinicalTrials.gov		144
3	Schizophrenia AND antihypertensives AND clinical trial	967	
	PubMed		57
	Embase		899
	ClinicalTrials.gov		11

3.2. Study characteristics

An overview of the characteristics of the included studies is provided in Table 2.

3.2.1.Study design

All included studies were parallel randomized trials and used a double-blind approach. A follow-up was also available in these studies [13–17].

Four out of five studies had SNP as intervention [13–16], and in one study, the intervention was telmisartan [17]. Both SNP and telmisartan interventions were compared to placebo. The treatment

duration was 2 weeks for two studies [15,16], 12 weeks for one study [17], and in two studies, the treatment consisted of one single dose of the experimental treatment [13,14].

3.2.2. Study population

The total number of participants was 162, in which 82 were in the experimental treatment group, and 80 in de placebo group. All studies included patients with schizophrenia [13–17], but two studies also included patients with schizoaffective disorder [14,17]. The baseline characteristics of the study population is shown in Table 3.

3.2.3. Outcomes

Three studies reported the Positive and Negative Syndrome Scale (PANSS) scores of all three subscales: PANSS general psychopathology (PANSS-G), PANSS positive (PANSS-P), and PANSS negative (PANSS-N) scale [14,15,17]. One study reported the total score of PANSS (PANSS-T), PANSS-P scores and PANSS-N scores [16], and one other study only reported the PANSS-N scores [13].

Other psychiatric outcome measures that were reported were Brief Psychiatric Rating Scale-18 (BPRS-18) for two studies [13,14], Cambridge Neuropsychological Test Automated Battery (CANTAB) Spatial Working Memory (SWM) tasks for one study [14], and one other study reported Scale for Assessment of Negative Symptoms (SANS), Calgary Depression Rating Scale (CDRS), and Quality of Life Scale (QLS) [17].

3.3. Risk of bias

The risk of bias for all included studies is summarized in Table 4. See Appendix B for the full assessment of the risk of bias, which includes judgements on each risk of bias domain.

3.3.1. Bias arising from the randomization process

An appropriate randomization process includes a clear description about the allocation sequence that is both random and concealed. Three studies mentioned the method that was used to achieve an appropriate randomization process, which led to a low risk of bias [14–16]. Two studies did not provide information about the method of concealing the allocation sequence, and therefore, a risk of bias of some concerns were given to these studies [13,17].

3.3.2. Bias due to deviations from intended interventions

Although all studies mentioned that their study was double-blinded, only four studies described the blinding procedure that resulted to a low risk of bias [13–16]. In one study, the blinding procedure was not described, which raised some concerns on the risk of bias [17].

3.3.3. Bias due to missing outcome data

All 5 studies analyzed a study population which is considered appropriate, meaning (nearly) all randomized participants were included in the analysis [13–17]. Besides, all studies provided explanations for exclusion of participants from the analysis if that was the case. Consequently, all studies were at low risk for bias due to missing outcome data.

3.3.4. Bias in measurement of the outcome

All studies used outcome measures that were appropriate, and the measurement of the outcome was consistent between intervention groups [13–17]. This contributed to a low risk of bias in measurement of the outcome.

3.3.5. Bias in selection of the reported result

None of the studies provided a statistical analysis plan, which raised some concerns on the risk of bias in selection of the reported results. However, all reported results were in accordance with the intended outcome measures for all studies [13–17]. In addition, all reported results for the outcome measurement corresponded to all intended analysis in one study [17].

3.3.6. Overall risk of bias

For all studies, an overall risk of bias was given following the Risk of Bias 2 Tool [12]. All studies had an overall risk of bias of "some concerns".

3.4. Effect of interventions

3.4.1. Main results

Figure 2 shows the results of the random-effects meta-analysis, that is forest plots for the mean differences of AHMs compared with placebo on all three PANSS subscales.

The pooled mean difference on the PANSS-G scale was -2.18 (95% CI: -3.91; -0.46), which was significant. This result indicates that AHM interventions led to an improvement in the general psychopathological symptoms of schizophrenia. Although the heterogeneity between studies was 0% ($p = 0.683$), this was not statistically significant. The prediction interval (PI: -13.38; 9.01) confirms heterogeneity between studies, since its range is much wider than the 95% CI, and therefore PI and 95% CI led to different conclusions. Altogether, we found no clear evidence on the improvement of the general psychopathological symptoms of schizophrenia by AHM interventions.

For the change in the PANSS-P scale, the pooled mean difference was -0.88 (95% CI: -1.66; -0.09), which was a considerable decrease. There was no heterogeneity between studies ($I^2 = 0\%$, $p = 0.920$), although this was not significant. The prediction interval (PI: -2.60; 0.84) is not much wider than the 95% CI, but the PI shows a chance of no statistically significant results, and no favorable effect

towards the AHM interventions. So, there is no clear evidence that there is a beneficial effect of AHM interventions on the positive symptoms in schizophrenia.

The pooled mean difference on the PANSS-N scores was -2.06 (95% CI: -4.42; 0.31), but not significant. The heterogeneity between studies was significantly high (I^2 = 84%, $p < 0.001$). The prediction interval (PI: -10.52; 6.41) and 95% CI led to different conclusions, since the range of the PI was much wider. Consequently, there is no sufficient evidence that AHM interventions would reduce the negative symptoms in schizophrenia.

3.4.2.Sensitivity analysis

We intended to conduct a sensitivity analysis based on the quality of the studies. However, all studies scored the same overall risk of bias, and therefore, there was no reason to conduct a sensitivity analysis based on the study quality.

Table 2. Study characteristics from selected studies.

Name (year)	Country	Study design	Condition	Treatment duration	Follow-up	Sample size	Intervention	Comparison	Outcome measure
Hallak (2013) [13]	Brazil	DB RD Parallel	Schizophrenia	Single dose treatment	Yes (4 weeks after infusion)	Treatment arm: 10 Placebo arm: 10	4-hour infusion of SNP 0.5 µg/kg/min	4-hour infusion of 5% glucose solution	PANSS-N, BPRS-18
Stone (2016) [14]	UK	DB RD Parallel	Schizophrenia or schizoaffective disorder	Single dose treatment	Yes (after infusion, and 4 weeks after treatment)	Treatment arm: 11 Placebo arm: 10	4-hour infusion of SNP 0.5 µg/kg/min diluted with isotonic 5% glucose solution	4-hour infusion of 0.5 µg/kg/min of isotonic 5% glucose solution	PANSS, BPRS-18, CANTAB SWM task
Wang (2018) [15]	China	DB RD Parallel	Schizophrenia	2 weeks	Yes (shortly after infusions and 4 weeks after end of treatment)	Treatment arm: 21 Placebo arm: 21	4-hour infusion of SNP 0.5 µg/kg/min	4-hour infusion of 5% glucose solution	PANSS
Brown (2019) [16]	US	DB RD Parallel	Schizophrenia	2 weeks	Yes (follow-up visit 1 week after infusion and at day 28)	Treatment arm: 18 Placebo arm: 18	4-hour infusion of SNP 0.5 µg/kg/min	4-hour infusion of dextrose 5% solution 0.5 µg/kg/min	PANSS
Fan (2017) [17]	US	DB RD Parallel	Schizophrenia or schizoaffective disorder	12 weeks	Yes (every 2 weeks)	Treatment arm: 22 Placebo arm: 21	Telmisartan 40 mg/day during first 2 weeks, and then 80 mg/day for the next 10 weeks	Placebo	PANSS, SANS, CDRS, QLS

DB: double-blind; RD: randomized; SNP: Sodium Nitroprusside; PANSS: Positive and Negative Syndrome Scale; PANSS-N: PANSS negative scale; BPRS-18: Brief Psychiatric Rating Scale 18; CANTAB: Cambridge Neuropsychological Test Automated Battery; SWM: Spatial Working Memory; SANS: Scale for Assessment of Negative Symptoms; CDRS: Calgary Depression Rating Scale; QLS: Quality of Life Scale.

Table 3. Baseline population characteristics of the selected studies.

	Hallak (2013) [13]	Stone (2016) [14]	Wang (2018) [15]	Brown (2019) [16]	Fan (2017) [17]
Participants					
Placebo arm	10	10	21	18	21
Male (%)	7 (70)	8 (80)	12 (57.14)	14 (77.78)	16 (76)
Female (%)	3 (30)	2 (20)	9 (42.86)	4 (22.22)	5 (24)
Treatment arm	10	10	21	18	22
Male (%)	7 (70)	7 (70)	11 (52.38)	14 (77.78)	18 (82)
Female (%)	3 (30)	3 (30)	10 (47.62)	4 (22.22)	4 (18)
Mean age (Y)					
Placebo	25.6 ± 3.9	40.0 ± 10.0	29.4 ± 7.5	40.4 ± 11.0	44.4 ± 11.5
Treatment	25.5 ± 6.7	34.0 ± 9.0	30.5 ± 7.3	47.1 ± 10.5	41.5 ± 12.3
Illness duration					
Placebo	38.4 ± 31.9 Mo	17 ± 8 Y	106.2 ± 78.9 Mo	NA	23.0 ± 5.7 Y
Treatment	34.2 ± 27.6 Mo	12 ± 7 Y	90.3 ± 59.8 Mo	NA	20.5 ± 5.2 Y

Mo: months; Y: years; NA: Not Assessed.

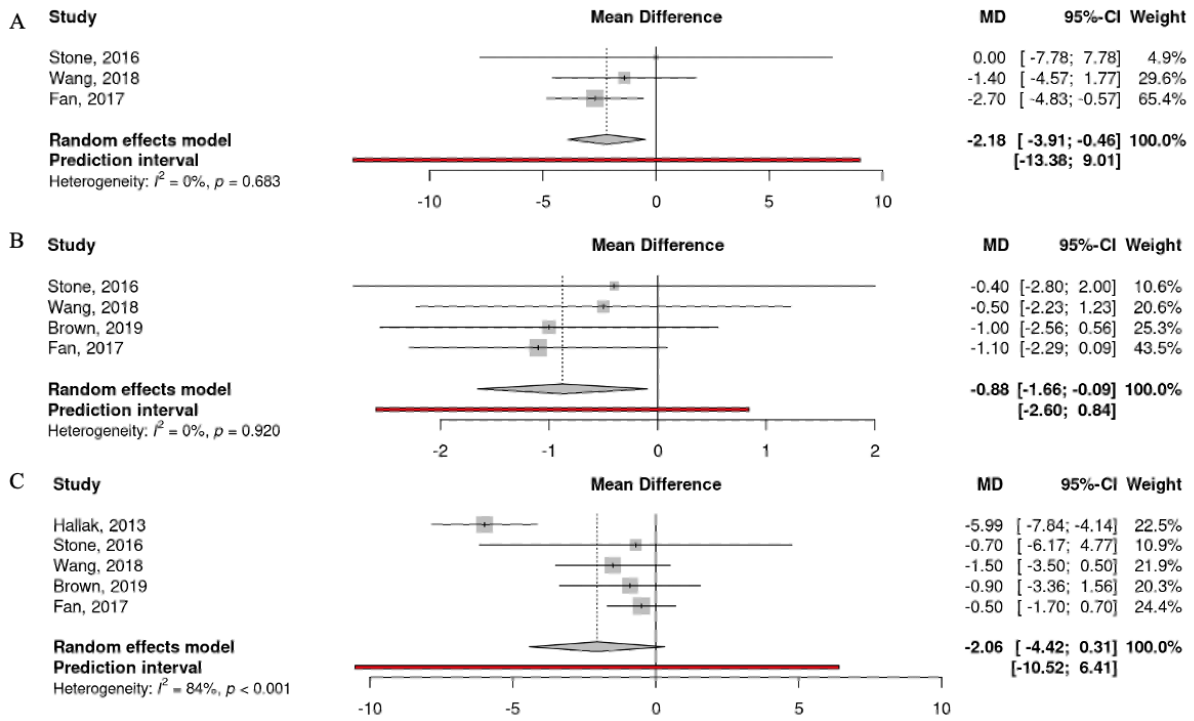

Figure 2. Forest plots for mean differences of AHMs compared to placebo on PANSS-G (A), PANSS-P (B), and PANSS-N scale (C).

Table 4. Risk of bias.

Study	1. Bias arising from the randomization process	2. Bias due to deviations from intended interventions	3. Bias due to missing outcome data	4. Bias in measurement of the outcome	5. Bias in selection of the reported result	**Overall**
Hallak 2013						
Stone 2016						
Wang 2018						
Brown 2019						
Fan 2017						

Green = low risk of bias; Yellow = some concerns; Red = high risk of bias.

4. Discussion

4.1. Main results

The suggestion of a potential benefit by drugs that block the angiotensin system in psychiatric disorders is not new. There was one meta-analysis by Brownstein et al. (2018) whereby the aim was to clarify the psychotropic potential of angiotensin agents. The results of the random-effects meta-analysis, which included 11 RCTs, showed an improvement in mental-related quality of life (QoL) in asymptomatic patients taking ACE inhibitors or AT_1R blockers. The mental-related QoL consisted of positive wellbeing, mental and anxiety domains [19]. Although these results were seen in asymptomatic patients, these findings indicate a potential positive effect on the mental health by ACE inhibitors and AT_1R blockers. Even though the outcome domains of the meta-analysis of Brownstein and colleagues differ from our outcome, which is improvement in symptoms of psychosis, an improvement in psychotic symptoms could also be associated with a better mental health. And as far as we know, there are no meta-analyses performed on the associations between the effects of AHM treatment and psychosis. So, this will be the first study to assess this relation.

In the group of all AHM treatments, we intended to compare AAs with non-AAs. However, this could not be carried out since only one study with an AA could be identified and included into the analysis. Therefore, we discuss the results in the light of the effect of all AHM interventions on psychosis. The results of the random-effects meta-analysis did not show clear evidence on the improvement of schizophrenia symptoms by AHM interventions compared to placebo. These results consisted of uncertainty due to heterogeneity and insufficient RCTs. In the analysis on the PANSS subscales, not all RCTs could be included because of non-reported data. Hallak et al. (2013) and Brown et al. (2019) did not report the PANSS-G scores and were not included in the analysis regarding the PANSS-G scale. Hallak and colleagues did also not report the PANSS-P scores, whereby the PANSS-P scale analysis did not include Hallak et al. (2013). Only the analysis of the PANSS-N scale comprised all included studies.

The results on the PANSS-G scale were based on only three out of five included studies, which contributes to the high uncertainty of the results. Therefore, we cannot draw conclusions based on these results. Hence, there is scarce evidence about the effect of AHM interventions on the general psychopathological symptoms in schizophrenia.

On the other hand, the results on the PANSS-N scale showed high heterogeneity with a wide PI and 95% CI. The high heterogeneity might be due to the mean difference of the study Hallak et al. (2013) which is an outlier. Therefore, we found no statistically significant evidence that AHM interventions reduced the negative symptoms in schizophrenia.

However, the results on the PANSS-P scale might be interesting to be further elaborated. This is because the pooled mean difference showed a considerable decrease in the PANSS-P scale with AHM interventions compared to placebo, and the 95% CI and PI did not differ much from each other,

contributing to a low heterogeneity. So, these results would suggest a trend towards a positive association between AHM interventions and the positive symptoms in schizophrenia.

4.1.1.Study population

Between studies, there were differences regarding the study population. Hallak et al. (2013) and Wang et al. (2018) had a study population of young participants with shorter duration of illness, while the other studies comprised of a population that was older and with a longer duration of illness. These differences can be found in Table 4. However, the influence of the study population on the results is unclear, since there is no consistent effect on the results due to the young study population with shorter duration of illness.

4.1.2.Treatment duration

The studies included for analysis differ in the treatment duration and number of infusions. Hallak et al. (2013) and Stone et al. (2016) conducted a study with a single dose of SNP, Wang et al. (2018) and Brown et al. (2019) had a treatment duration of 2 weeks, and Fan et al. (2017) had a 12-week treatment duration. Indeed, this inconsistency in treatment duration could influence the results.

4.2. Data-extraction

4.2.1.Study design

Even though all studies had a parallel study design, Brown et al. (2019) used an adaptive parallel design, named Sequential Parallel Comparison Design (SPCD). This study design reduces placebo response rate and sample size requirement. The study consisted of two treatment phases and three treatment arms. The first arm consisted of participants who were treated with SNP in both phases (SNP-SNP), the second arm were participants who received placebo in the first phase and SNP in the second phase (placebo-SNP), and the third arm consisted of participants who were treated with placebo in both phases (placebo-placebo). After phase 1, participants who were allocated in the SNP-SNP group were excluded from phase 2 analysis, and only placebo non-responders were re-randomized to phase 2. Subsequently, the number of randomized participants into phase 2 was decreased. Therefore, we chose to only include the data of participants in phase 1. Also, we only considered the data of the SNP-SNP and placebo-placebo groups.

4.2.2.Psychiatric outcome measure

The only primary outcome measure that was common between all included studies was the PANSS. PANSS constitutes of three subscales: general psychopathology scale, positive scale, and negative scale. These scales together form a total score of the PANSS. Raw data of the baseline and post-treatment PANSS scores, and/ or the mean difference of PANSS scores between post-treatment and baseline were

extracted from the study. However, there were some inconsistencies between studies regarding measuring PANSS as outcome.

Brown et al. (2019) have reported scores on PANSS-T, PANSS-P, and PANSS-N, but no scores on PANSS-G. Therefore, the corresponding author was contacted to collect the PANSS-G scores, but without success. Consequently, this study could not be included in the analysis on the PANSS-G scale.

Hallak et al. (2013) only made use of the negative subscale of the PANSS, and therefore this study was only included in the analysis regarding the PANSS-N scale. Besides, there were no raw data of the PANSS-N scores available in the study, but instead, the PANSS-N scores were shown in a graph from baseline to week 4. Hence, we tried to contact the first author, but failed to receive the raw data. Therefore, we used WebPlotDigitizer to extract the data from the graph. We only extracted the value at baseline and at week 4 for both SNP and placebo interventions. This way of data extraction was manually, which made the obtained data not accurate. For this reason, the data extraction was done two times, subsequently, the mean was taken for the ultimate PANSS-N scores.

All studies reported PANSS scores at baseline and after treatment. Stone et al. (2016) and Wang et al. (2018) also reported follow-up PANSS scores, while other studies did not. For this reason, the follow-up PANSS scores were not included in the analysis. Accordingly, we could not assess the long-term effect AHMs interventions on psychosis.

In the study of Wang et al. (2018), participants received two infusions with an interval of one week. PANSS scores were measured at baseline, after the first and second infusion, and at follow-up. We chose to only include the PANSS scores after the second infusion, because then the full treatment was finished, and these scores are more representative for the post-treatment PANSS scores.

4.3. Limitations

While we have searched three great databases for including the utmost extent of RCTs, we could only include 5 RCTs into the analysis. Also, the systematic review was focused on all AHMs, but we only identified two AHM treatments, namely SNP and telmisartan. From the 5 RCTs, there was only one about an angiotensin agent, and the other 4 were about SNP. Treatment durations varied among the studies, as well as some outcome measures. PANSS-G was only reported by three studies, whereas PANSS-P was reported by four, increasing the overall weight of each study in the final result. Additionally, those were small sample-sized RCTs, which can undermine internal and external validities of the results by over- or under-estimating its impact in the overall population (reducing data generalizability).

4.4. Implications

There is no great body of evidence on the association between the effects of AHMs and psychosis. To further investigate a possible association between the positive symptoms of schizophrenia and AHMs,

new clinical trials with bigger sample sizes are needed. It would also be interesting if these new RCTs used the AHMs in a design that would resemble more a real-life situation, that is, as an add-on-therapy to previous the patients' baseline antipsychotic treatment (as some of the authors already did).

5. Conclusion

The low number of RCTs available, their small sample size and heterogenous methodology comprise the generalizability of our results. Even though no clear statistical significance was identified, positive symptoms showed a trend towards improvement with AHMs. This could be a starting point for developing further RCTs with bigger sample size to elucidate the role of AHMs in modulating these positive symptoms in schizophrenic patients.

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Appendices

A. Quantitative analysis

First, we extracted the mean and standard deviation of all reported PANSS scores at baseline and post-treatment, and/ or the mean difference of the PANSS scores between post-treatment and baseline if reported. If not reported, we calculated it ourselves by subtracting the baseline PANSS score from the post-treatment PANSS score. Here, a negative mean difference reflects a decrease in the PANSS scale, and a positive mean difference means an increase in the PANSS scale (Table A.1). Afterwards, the mean difference and standard deviation between treatment and placebo were calculated. The standard deviation was calculated using the following formula: $SD_3 = \sqrt{{SD_1}^2 + {SD_2}^2}$. From here, we could calculate the 95% confidence interval for the mean difference between treatment and placebo (Table A.2). The formula for the 95% confidence interval is as follows: 95% $CI = \bar{x} \pm z \times \frac{s}{\sqrt{n}}$, where $\bar{x}$ is the mean, z is the z-value of the 95% confidence interval, that is 1.96, s is the standard deviation, and n is the sample size. Eventually, the data in Table A.2. were used for the random-effects meta-analysis in Easymeta.

Table A.1. Mean and standard deviation of the PANSS-scores.

	Hallak 2013	**Stone 2016**	**Wang 2018**	**Brown 2019**	**Fan 2017**
Baseline PANSS					
General scale					
Placebo	NA	34.5 ± 8.4	32.4 ± 2.7	NA	34.1 ± 10
Treatment	NA	37.0 ± 9.7	34.5 ± 7.2	NA	34.6 ± 6.8
Positive scale					
Placebo	NA	23.6 ± 2.5	21.3 ± 2.9	22.5 ± 3.2	16.4 ± 7.6
Treatment	NA	22.3 ± 1.8	20.5 ± 2.7	24.9 ± 3.5	16.7 ± 5.5
Negative scale					
Placebo	29.44 ± 2.11	20.1 ± 6.6	24.4 ± 2.5	21.4 ± 4.6	20.0 ± 5.5
Treatment	29.11 ± 2.3	21.4 ± 6.3	23.0 ± 2.6	20.9 ± 5.5	19.9 ± 6.5
Post-treatment PANSS					
General scale					
Placebo	NA	32.0 ± 8.0	32.0 ± 3.0	NA	NA
Treatment	NA	34.5 ± 10.2	32.7 ± 6.5	NA	NA
Positive scale					
Placebo	NA	21.7 ± 4.0	19.0 ± 2.6	21.3 ± 3.6	NA
Treatment	NA	20.0 ± 2.5	17.7 ± 3.2	23.1 ± 4.6	NA
Negative scale					
Placebo	28.21 ± 2.13	18.2 ± 6.1	23.2 ± 3.3	19.8 ± 5.1	NA
Treatment	21.89 ± 1.87	18.8 ± 6.6	20.3 ± 4.5	19.1 ± 4.7	NA
Mean difference (post-treatment – baseline)					
General scale					
Placebo	NA	-2.5 ± 11.6	-0.4 ± 4.04	NA	0.3 ± 4.7
Treatment	NA	-2.5 ± 14.08	-1.8 ± 9.7	NA	-2.4 ± 5.4
Positive scale					
Placebo	NA	-1.9 ± 4.7	-2.3 ± 3.89	-1.3 ± 4.75	-0.1 ± 3.1
Treatment	NA	-2.3 ± 3.08	-2.8 ± 4.19	-1.8 ± 5.78	-1.2 ± 2.5
Negative scale					
Placebo	-1.23 ± 3.00	-1.9 ± 8.99	-1.2 ± 4.14	-1.6 ± 6.87	0.1 ± 2.8
Treatment	-7.22 ± 2.96	-2.6 ± 9.12	-2.7 ± 5.2	-1.8 ± 7.23	-0.4 ± 2.9

Mean difference (treatment – placebo)					
General scale	NA	0 ± 18.24	-1.4 ± 10.51	NA	-2.7 ± 7.16
Positive scale	NA	-0.4 ± 5.63	-0.5 ± 5.72	-1 ± 3.38	-1.1 ± 3.98
Negative scale	-5.99 ± 4.22	-0.7 ± 12.81	-1.5 ± 6.64	-0.9 ± 5.05	-0.5 ± 4.03

PANSS: Positive and Negative Syndrome Scale; NA: Not Assessed.

Table A.2. Mean difference (95% CI) for each PANSS subscale.

	Hallak 2013	**Stone 2016**	**Wang 2018**	**Brown 2019**	**Fan 2017**
PANSS-G	NA	0 (-7.80; 7.80)	-1.4 (-4.58; 1.78)	NA	-2.7 (-4.84; -0.56)
PANSS-P	NA	-.4 (-2.81; 2.01)	-0.5 (-2.23; 1.23)	-1 (-2.56; 0.56)	-1.1 (-2.29; 0.09)
PANSS-N	-5.99 (-7.84; -4.14)	-0.7 (-6.18; 4.78)	-1.5 (-3.51; 0.51)	-0.9 (-3.37; 1.57)	-0.5 (-1.70; 0.70)

PANSS-G: PANSS-General psychopathology scale; PANSS-P: PANSS-Positive scale; PANSS-N: PANSS-Negative scale; NA: Not Assessed.

B. Risk of Bias assessment

This appendix provides the full assessment of the risk of bias for all included studies. The domains and signaling questions are copied from the Supplementary material of the Cochrane Risk of Bias 2 Tool [12] and are provided with responses based on our option with direct quotes from the study publication and/ or supplementary document(s), and if necessary, clarification regarding the given response. For elaborations of the signaling questions, see the Supplementary material of the Cochrane Risk of Bias 2 Tool [12].

Table B. Decisions on the Risk of Bias assessment of the included studies.

Study	Domain	Signaling question	Response	Quotes (and clarification)
Hallak et al. 2013	1 Bias arising from the randomization process	1.1. Was the allocation sequence random?	Y	"Patients were randomly assigned using a pseudorandomization process to either SNP or placebo group (allocation ratio. 1:1)."
		1.2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	"The randomization code was generated by a research assistant at the university hospital." There is no information about the relationship of the research assistant with the trial. We don't know if the research assistant is dependent of independent of the research group.
		1.3. Did baseline differences between intervention groups suggest a problem with the randomization process?	N	"There were no statistical differences in age, years of education, length of illness, number of hospitalizations, sex, and marital status of patient groups receiving sodium nitroprusside or placebo."
		Risk of bias judgement		Some concerns
	2 Bias due to deviations from the intended	2.1. Were participants aware of their assigned intervention during the trial?	N	"The experiment was a double-blind, placebo-controlled trial."
		2.2. Were carers and people delivering the interventions aware of	N	"Experimental infusion standards and conditions were identical for both infusion (SNP and placebo)

	interventions (*effect of assignment to intervention*)	participants' assigned intervention during the trial?		groups, and both patients and front-line study staff were masked to the assigned intervention."
		2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	NA	NA
		2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	NA
		2.5. If Y/PY to 2.4: Were these deviations from intended intervention balanced between groups?	NA	NA
		2.6. Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	We can assume an ITT-analysis by the following: "All participants who were randomized completed the study procedures, and all patient data from randomized participants were included in the final analysis."
		2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	NA
		Risk of bias judgement		Low
	3 Bias due to missing outcome data	3.1. Were data for this outcome available for all, or nearly all, participants randomized?	Y	"All participants who were randomized completed the study procedures, and all patient data from randomized participants were included in the final analysis."
		3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	NA	NA

		3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	NA
		3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	NA
		Risk of bias judgement		Low
	4 Bias in measurement of the outcome	4.1. Was the method of measuring the outcome inappropriate?	N	"The PANSS is commonly used in clinical trials. It includes 7 positive subscale items, 7 negative subscale items, and 16 gen- eral psychopathology items. […] The PANSS uses a 7-point severity scale (1, absent;2, minimal;3, mild;4, moderate;5, moderate-severe; 6, severe;7, extreme)."
		4.2. Could measurement or ascertainment of the outcome have differed between intervention groups?	N	For both intervention groups, the same measurement methods and thresholds are used, at comparable time points.
		4.3. If N/ PN/ NI to 4.1. and 4.2.: Were outcome assessors aware of the intervention received by study participants?	N	"Experimental infusion standards and conditions were identical for both infusion groups, and both patients and frontline study staff were masked to the assigned intervention."
		4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	NA
		4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	NA
		Risk of bias judgement		Low

	5 Bias in selection of the reported result	5.1. Were the data that produced this result analyzed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	There was no pre-specified analysis plan or other supplementary documents available that would inform us to assess this domain.
		Is the numerical result being assessed likely to have been selected, on the basis of the results, from…		
		5.2. … multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	We believe that all eligible reported results for the outcome domain correspond to all intended outcome measurements.
		5.3. … multiple eligible analyses of the data?	NI	There was no pre-specified analysis plan or other supplementary documents available that would inform us to assess this domain.
		Risk of bias judgement		Some concerns
Stone et al. 2016	1 Bias arising from the randomization process	1.1. Was the allocation sequence random?	Y	"Randomization of participants was via an independent web-based service hosted at the King's Clinical Trials Unit (http://www.ctu.co.uk). Participants were randomized 1:1 to SNP or placebo using the method of block randomization, with randomly varying block sizes of 2 and 4."
		1.2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	"Researchers entered the participants detail to the randomization and received an automatic blinded confirmation email that randomization had occurred. Unblinded emails were automatically sent to the dispensing pharmacists, with details of treatment allocation. The pharmacy issued either SNP solution and isotonic 5% glucose solution or isotonic 5% glucose solution only (i.e. placebo) in accordance

			with the randomization email. In the case of SNP treatment, an unblinded clinical research nurse diluted the SNP with isotonic glucose solution to achieve the required dose of SNP to be delivered over 4h. The prepared solution or placebo was concealed in an opaque encasing to protect the SNP from ultraviolet light and to ensure blinding of the study team. The infusion was run at a rate to achieve 0.5 µg/kg per min (SNP) or the equivalent volume-per-minute infusion rate for placebo over the course of 4h. The unblinded clinical research nurse did not take part in any of the ratings."
	1.3. Did baseline differences between intervention groups suggest a problem with the randomization process?	N	"Participants were well matched for demographic details."
	Risk of bias judgement		Low
2 Bias due to deviations from the intended interventions (*effect of assignment to intervention*)	2.1. Were participants aware of their assigned intervention during the trial?	N	"This was a double-blind, placebo-controlled clinical trial."
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	"The prepared solution or placebo was concealed in an opaque encasing to protect the SNP from ultraviolet light and to ensure blinding of the study team."
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	NA	NA

		2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	NA
		2.5. If Y/PY to 2.4: Were these deviations from intended intervention balanced between groups?	NA	NA
		2.6. Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	"Twenty-one were randomized. One subject was excluded from analysis after randomization because their PANSS Positive subscale score was <20 at the time of starting the infusion (Fig. 1)."
		Risk of bias judgement		Low
	3 Bias due to missing outcome data	3.1. Were data for this outcome available for all, or nearly all, participants randomized?	Y	"Twenty-one were randomized. One subject was excluded from analysis after randomization because their PANSS Positive subscale score was <20 at the time of starting the infusion (Fig. 1)."
		3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	NA	NA
		3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	NA
		3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	NA
		Risk of bias judgement		Low
	4	4.1. Was the method of measuring the outcome inappropriate?	N	"The participants then underwent psychiatric evaluation including assessment with PANSS and BPRS-18."

	Bias in measurement of the outcome	4.2. Could measurement or ascertainment of the outcome have differed between intervention groups?	N	For both intervention groups, the same measurement methods and thresholds are used, at comparable time points.
		4.3. If N/ PN/ NI to 4.1. and 4.2.: Were outcome assessors aware of the intervention received by study participants?	NI	There is no information about the outcome assessors.
		4.4. If Y/PY/NI to 4.3.: Could assessment of the outcome have been influenced by knowledge of intervention received?	N	"This was a double-blind, placebo-controlled clinical trial." "The prepared solution or placebo was concealed in an opaque encasing to protect the SNP from ultraviolet light and to ensure blinding of the study team."
		4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	NA
		Risk of bias judgement		Low
	5 Bias in selection of the reported result	5.1. Were the data that produced this result analyzed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	There was no pre-specified analysis plan or other supplementary documents available that would inform us to assess this domain.
		Is the numerical result being assessed likely to have been selected, on the basis of the results, from…		
		5.2. … multiple eligible outcome measurements (e.g. scales,	N	We believe that all eligible reported results for the outcome domain correspond to all intended outcome measurements.

		definitions, time points) within the outcome domain?		
		5.3. … multiple eligible analyses of the data?	NI	There was no pre-specified analysis plan or other supplementary documents available that would inform us to assess this domain.
		Risk of bias judgement		Some concerns
Wang et al. 2018	1 Bias arising from the randomization process	1.1. Was the allocation sequence random?	Y	"Participants were randomized 1:1 to SNP or placebo arms using a random number table."
		1.2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	"Experimental infusion standards and conditions were identical for both groups, and both patients and front-line study staff were blind to the assigned in- tervention. An unblinded clinical research nurse diluted the SNP with isotonic glucose solution to achieve the required dose, but this nurse did not undertake any other task in the study. The prepared solution or placebo was wrapped in opaque packages to protect the SNP from ul- traviolet light and ensure blinding of the study team."
		1.3. Did baseline differences between intervention groups suggest a problem with the randomization process?	N	"Baseline clinical and demographic details were well matched between placebo and SNP groups (Fig. 1), with no significant differences in age, sex, ratio, years of education, length of illness, smoking status, number of hospitalizations, marital status, and native place between groups."
		Risk of bias judgement		Low
	2 Bias due to deviations from the	2.1. Were participants aware of their assigned intervention during the trial?	N	"This was a randomized double-blind, placebo-controlled clinical trial." "Experimental infusion standards and conditions were identical for both groups, and both patients and

	intended interventions (*effect of assignment to intervention*)		front-line study staff were blind to the assigned intervention."
		2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	"Experimental infusion standards and conditions were identical for both groups, and both patients and front-line study staff were blind to the assigned intervention." "The prepared solution or placebo was wrapped in opaque packages to protect SNP from ultraviolet light and ensure blinding of the study team."
		2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	NA	NA
		2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	NA
		2.5. If Y/PY to 2.4: Were these deviations from intended intervention balanced between groups?	NA	NA
		2.6. Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	Figure 1 shows that 42 randomized participants are all included in the analysis (ITT).
		Risk of bias judgement		Low
	3 Bias due to missing outcome data	3.1. Were data for this outcome available for all, or nearly all, participants randomized?	Y	Figure 1 shows that 42 randomized participants are all included in the analysis.
		3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	NA	NA

		3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	NA
		3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	NA
		Risk of bias judgement		Low
	4 Bias in measurement of the outcome	4.1. Was the method of measuring the outcome inappropriate?	N	"Participants underwent psychiatric evaluation using the PANSS."
		4.2. Could measurement or ascertainment of the outcome have differed between intervention groups?	N	For both intervention groups, the same measurement methods and thresholds are used, at comparable time points.
		4.3. If N/ PN/ NI to 4.1. and 4.2.: Were outcome assessors aware of the intervention received by study participants?	NI	There is no information about the outcome assessors.
		4.4. If Y/PY/NI to 4.3.: Could assessment of the outcome have been influenced by knowledge of intervention received?	N	"This was a randomized double-blind, placebo-controlled clinical trial." "Experimental infusion standards and conditions were identical for both groups, and both patients and front-line study staff were blind to the assigned intervention."
		4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	NA
		Risk of bias judgement		Low

	5 Bias in selection of the reported result	5.1. Were the data that produced this result analyzed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	There was no pre-specified analysis plan or other supplementary documents available that would inform us to assess this domain.
		Is the numerical result being assessed likely to have been selected, on the basis of the results, from…		
		5.2. … multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	We believe that all eligible reported results for the outcome domain correspond to all intended outcome measurements.
		5.3. … multiple eligible analyses of the data?	NI	There was no pre-specified analysis plan or other supplementary documents available that would inform us to assess this domain.
		Risk of bias judgement		Some concerns
Brown et al. 2019	1 Bias arising from the randomization process	1.1. Was the allocation sequence random?	Y	"The clinical trials management software generated a randomization identifier for each participant." "Participants who met eligibility criteria were randomized in 1:1:1 ratio to 1 of 3 treatment sequences as follows: SNP and SNP, placebo and SNP, and placebo and placebo.". Supplement 1. Trial Protocol: "The randomization scheme will be programmed into the CTMS software and will generate a randomization code for each subject upon enrollment into the study."
		1.2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	"The clinical trials management software generated a randomization identifier for each participant; the identifier was accessible to the site pharmacy and

			was used to prepare the corresponding infusion treatment." Supplement 1. Trial Protocol: "The Institutional Pharmacy will issue either undiluted sodium nitroprusside in sterile 5% dextrose or sterile 5% dextrose only. […] A study label that includes the subject ID and randomization ID will be pasted to the foil bag so that it is clearly visible. The dextrose solution will also be covered with an identical foil bag and stud label so that medical personal administering the i.v. will be blinded to the study treatment. […] No members of the study team at study sties, will have access to the randomization scheme during the conduct of the study, with the exception of the Site's unblinded pharmacists or nurse as designated by the PI."
	1.3. Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	Table 1 provides the baseline clinical and demographic characteristics. The groups seem well-distributed.
	Risk of bias judgement		Low
2 Bias due to deviations from the intended interventions (*effect of assignment to intervention*)	2.1. Were participants aware of their assigned intervention during the trial?	N	"Both participants and clinicians were blinded to treatment." They used placebo as comparative intervention. Supplement 1. Trial Protocol: "The investigator, subject, and study staff will be blinded. The preparation and labeling of the study drugs will be performed by the site pharmacy in a way to ensure blinding throughout the study."

	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	"Both participants and clinicians were blinded to treatment." Supplement 1. Trial Protocol: "A study label that includes the subject ID and randomization ID will be pasted to the foil bag so that it is clearly visible. The dextrose solution will also be covered with an identical foil bag and study label so that medical personal administering the i.v. will be blinded to the study treatment."
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	NA	NA
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	NA
	2.5. If Y/PY to 2.4: Were these deviations from intended intervention balanced between groups?	NA	NA
	2.6. Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	"A modified intent-to-treat analysis was used (ie, only including participants who at least started the infusion), and per the SPCD design, only placebo nonresponders were included in the phase 2 analyses, whereas all participants from phase 1 were included." Supplement 1. Trial Protocol: "The ITT population is defined as all randomized subjects. The ITT population will be the primary population for the analysis of the primary, secondary, and additional efficacy endpoints."

		Risk of bias judgement		Low
	3 Bias due to missing outcome data	3.1. Were data for this outcome available for all, or nearly all, participants randomized?	Y	"Fifty participants (96%) completed phase 1; 2 participants terminated the study early. Of these 50 participants, 32 were included in the phase 2 outcome analyses as placebo nonresponders. […] Of the 32 participants who entered phase 2, 30 (94%) completed phase 2." Both number of patients that are included in the analyses are around 95%, which is sufficient. Besides, reasons for exclusion were reported.
		3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	NA	NA
		3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	NA
		3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	NA
		Risk of bias judgement		Low
	4 Bias in measurement of the outcome	4.1. Was the method of measuring the outcome inappropriate?	N	"The primary outcome measures examined were the PANSS total, positive, and negative scores with SNP compared with placebo across each 2-week phase."
		4.2. Could measurement or ascertainment of the outcome have differed between intervention groups?	N	For both intervention groups, the same measurement methods and thresholds are used, at comparable time points.
		4.3. If N/ PN/ NI to 4.1. and 4.2.: Were outcome assessors aware of the	N	"A confirmation of both schizophrenia diagnosis and symptom severity was carried out by an independent,

		intervention received by study participants?		expert clinician remote rater form Massachusetts General Hospital (H.E.B.).” Supplement 1. Trial Protocol: “During the infusion visits, the study staff conducting the clinical efficacy assessments must not be able to view the bag containing the infusion solution to ensure that they remain blinded. The bag must be protected from view with an opaque covering.”
		4.4. If Y/PY/NI to 4.3.: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	NA
		4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	NA
		Risk of bias judgement		Low
	5 Bias in selection of the reported result	5.1. Were the data that produced this result analyzed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	There was no pre-specified analysis plan or other supplementary documents available that would inform us to assess this domain.
		Is the numerical result being assessed likely to have been selected, on the basis of the results, from…		
		5.2. … multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	We believe that all eligible reported results for the outcome domain correspond to all intended outcome measurements.

		5.3. … multiple eligible analyses of the data?	NI	There was no pre-specified analysis plan or other supplementary documents available that would inform us to assess this domain.
		Risk of bias judgement		Some concerns
Fan et al. 2017	1 Bias arising from the randomization process	1.1. Was the allocation sequence random?	Y	"After screening, subjects were randomized to either telmisartan or placebo in a double-blind fashion based on a permuted block design with block size of six."
		1.2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	"Subjects met with the research team every 2 weeks. […] Study medication was dispensed during each visit." They did not specify who was responsible for dispensing study medication, and how this was done.
		1.3. Did baseline differences between intervention groups suggest a problem with the randomization process?	N	"There were no significant differences between the two groups in age, gender, race, marital status, diagnosis (schizophrenia or schizoaffective disorder), clozapine or olanzapine treatment ($p > 0.30$)."
		Risk of bias judgement		Some concerns
	2 Bias due to deviations from the intended interventions (*effect of assignment to intervention*)	2.1. Were participants aware of their assigned intervention during the trial?	N	"After screening, subjects were randomized to either telmisartan or placebo in a double-blind fashion."
		2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	NI	"After screening, subjects were randomized to either telmisartan or placebo in a double-blind fashion." Beside mentioning this, they did not further describe how the procedure of double-blinding was done.
		2.3. If Y/PY/NI to 2.1. or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	NI	There is no information about this.

		2.4. If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	NA
		2.5. If Y/PY to 2.4: Were these deviations from intended intervention balanced between groups?	NA	NA
		2.6. Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	"The statistical analysis was primarily focused on those participants who completed the study (completers), follow by ITT analysis with last observation carried forward (LOCF)."
		Risk of bias judgement		Some concerns
	3 Bias due to missing outcome data	3.1. Were data for this outcome available for all, or nearly all, participants randomized?	Y	"Sixty-six subjects were screened. Among those, 62 were enrolled and 54 were randomized (26 in the telmisartan groups, 28 in the placebo group). Forty-three patients completed the study (22 in the telmisartan group, 21 in the placebo group) and were included in the final data analysis (Fig. 1)." So, 43 out of 54 randomized participants were analyzed (79,63%). This is not sufficient, but they mentioned the reason of exclusion in Figure 1.
		3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	NA	NA
		3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	NA
		3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	NA
		Risk of bias judgement		Low

	4 Bias in measurement of the outcome	4.1. Was the method of measuring the outcome inappropriate?	N	"Eligible subjects completed an assessment which included the PANSS."
		4.2. Could measurement or ascertainment of the outcome have differed between intervention groups?	N	For both intervention groups, the same measurement methods and thresholds are used, at comparable time points.
		4.3. If N/ PN/ NI to 4.1. and 4.2.: Were outcome assessors aware of the intervention received by study participants?	PN	There is no information about the outcome assessor in the paper, however, their trial is registered in ClinicalTrials.gov (identifier: NCT00981526), and there it is mentioned that a quadruple masking of participant, care provider, investigator, and outcome assessor was done.
		4.4. If Y/PY/NI to 4.3.: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	NA
		4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	NA
		Risk of bias judgement		Low
	5 Bias in selection of the reported result	5.1. Were the data that produced this result analyzed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	There was no pre-specified analysis plan or other supplementary documents available that would inform us to assess this domain.
		Is the numerical result being assessed likely to have been selected, on the basis of the results, from…		

		5.2. … multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	We believe that all eligible reported results for the outcome domain correspond to all intended outcome measurements.
		5.3. … multiple eligible analyses of the data?	N	We believe that all eligible reported results for the outcome measurement correspond to all intended analyses.
		Risk of bias judgement		Some concerns
Adelino et al. 2021	1 Bias arising from the randomization process	1.1. Was the allocation sequence random?	NI	"This was a double-blind, randomized, placebo-controlled clinical trial." Next to mentioning that the study is randomized, there is no further elaboration about the randomization process.
		1.2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	There is no information about concealing the allocation sequence.
		1.3. Did baseline differences between intervention groups suggest a problem with the randomization process?	N	"Groups were matched for age, gender and severity of illness."
		Risk of bias judgement		Some concerns
	2 Bias due to deviations from the intended interventions (*effect*	2.1. Were participants aware of their assigned intervention during the trial?	N	"This was a double-blind, randomized, placebo-controlled clinical trial." Placebo is used as a comparative intervention.
		2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	NI	Beside mentioning a double-blind trial, there is no information about its process.

	of assignment to intervention)	2.3. If Y/PY/NI to 2.1. or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	NI	There is no information about this.
		2.4. If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	NA
		2.5. If Y/PY to 2.4: Were these deviations from intended intervention balanced between groups?	NA	NA
		2.6. Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	"All participants completed the study." "No subject needed to suspend the infusion or withdrew from the study."
		Risk of bias judgement		Some concerns
	3 Bias due to missing outcome data	3.1. Were data for this outcome available for all, or nearly all, participants randomized?	Y	"All participants completed the study." "No subject needed to suspend the infusion or withdrew from the study."
		3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	NA	NA
		3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	NA
		3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	NA
		Risk of bias judgement		Low
	4	4.1. Was the method of measuring the outcome inappropriate?	N	"Severity of symptoms were assessed by using PANSS, BPRS-18, and CGI scales."

	Bias in measurement of the outcome	4.2. Could measurement or ascertainment of the outcome have differed between intervention groups?	N	For both intervention groups, the same measurement methods and thresholds are used, at comparable time points.
		4.3. If N/ PN/ NI to 4.1. and 4.2.: Were outcome assessors aware of the intervention received by study participants?	NI	There is no information about the outcome assessors.
		4.4. If Y/PY/NI to 4.3.: Could assessment of the outcome have been influenced by knowledge of intervention received?	N	Placebo was used, which means that the participants were blinded.
		4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	NA
		Risk of bias judgement		Low
	5 Bias in selection of the reported result	5.1. Were the data that produced this result analyzed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	We could not obtain the trial protocol or other supplementary documents that would inform us to assess this domain.
		Is the numerical result being assessed likely to have been selected, on the basis of the results, from…		
		5.2. … multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	We believe that all eligible reported results for the outcome domain correspond to all intended outcome measurements.

	5.3. … multiple eligible analyses of the data?	N	We believe that all eligible reported results for the outcome measurement correspond to all intended analyses.
	Risk of bias judgement		Some concerns