THE PAC-INDEX: AN UPDATE

Shared Decision-Making in Choosing an Antipsychotic Agent

"How can the available evidence on cariprazine, brexpiprazol and amisulpride best be applied to aid patients suffering from non-affective psychosis in their choice of an antipsychotic agent?"

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Abbreviations

PAC-Index: Personal Antipsychotic Choice Index
CAR: cariprazine
BRE: brexpiprazole
AMI: amisulpride
SPC: Summary of Product Characteristics
EPS: Extrapyramidal Symptoms
RCT: Randomized Controlled Trial
NIMH: National Institute of Mental Health
PDSP: Psychoactive Drug Screening Program
MD: Mean Difference
SMD: Standardised Mean Difference
RR: Relative Risk
LoE: Level of confidence in Evidence
CI: Confidence Interval

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ABSTRACT

Introduction: In 2016, an online decision aid was developed to involve patients with a psychotic disorder in shared decision-making regarding the choice for antipsychotic medication. The tool combines the needs of the patient, indicated by the patient on a 5 -point Likert scale, with evidence-based ranking of risks or probabilities on a set of criteria. Criteria, based on patient panels, were: effectiveness concerning psychotic, depressive and cognitive symptoms, weight gain, sexual dysfunction, sedation, hypersomnia, extrapyramidal symptoms, anticholinergic adverse effects, hypersalivation, nausea, dizziness, fatigue and blunted affect/less need for companionship. The tool produces a personalised ranking of antipsychotic agents that matches the patients' preferences. The aim of this paper is to update the tool by adding caripiprazine and brexpiprazol and refining the ranking of amisulpride.

Method: A systematic search was performed in PubMed, EMBASE and Cochrane. Effect sizes from meta-analyses, receptor affinities and summaries of product characteristics were used to rank the antipsychotics per criterion. Updates were applied to the originally included agents where necessary. The rankings were tested in an expert panel of clinicians to translate the evidence-based data into clinical use.

Results: High-level evidence was available for ranking weight gain, sedation, sexual dysfunction, menstrual disorders, extrapyramidal symptoms, anticholinergic side effects and effectiveness for psychotic and depressive symptoms for all antipsychotic agents, including the newer ones. There was lower-level evidence ranking the remaining criteria.

Discussion & conclusion: A comprehensive update was devised in a systematic approach, resulting in an applicable tool for shared-decision making for current prescription tendencies.

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1. INTRODUCTION

Non-adherence is thought to be a major problem in the pharmaceutical treatment of patients with schizophrenia or schizophrenia-related diagnoses. One systematic review reports a mean non-adherence rate of 49.5%, defined as taking medication <75% of the time.[1] A recent retrospective chart review finds 31.7% of primary non-adherence, defined as not collecting a pharmacy prescription at least once in the last year.[2] Non-adherence or discontinuation increases the risk of relapse, hospitalization, and self-harm, and increases inpatients costs.[3] It is hypothesized that more involvement in the decision-making process can ultimately improve a patient's medication adherence. Research has demonstrated that electronic decision support systems can improve patient knowledge and subsequently can improve the quality of shared decision-making.[4] Additionally, it has been established that patients with psychotic disorders are willing to use these online aids.[5] To that extent, *van Dijk et al*. developed an online tool in 2016, the "*Personal Antipsychotic Choice Index*" (PAC Index).[6] The tools objective is to involve patients with a non-affective schizophrenia spectrum disorder, such as schizophrenia or schizoaffective disorder, in decision-making concerning their medication. Patients indicate for 20 adverse/intended effects how unacceptable or important it is to them. An algorithm then calculates which antipsychotic agent best suits their preference. Since its launch, the PAC-index has been used over 13.000 times.

Originally included were the 13 most frequently prescribed antipsychotic agents in the Netherlands, (quetiapine,

risperidone, olanzapine, haloperidol, clozapine, pipamperone, aripiprazole, zuclopenthixol, pimozide, penfluridol, sulpiride, flupentixol, and perphenazine), based on prescription data from the Drug Information System of the Dutch National Healthcare Institute, as well as 2 anticipated medications (lurasidone and amisulpride). Evidence on these agents were evaluated per effect, selected by patient panels. Criteria of the PAC-index were defined as follows: (1) weight gain, (2) sexual dysfunction, (3) drowsiness i.e. sedation/somnolence, (4) sleep problems, (5) extrapyramidal side-effects (EPS) defined as use of anti-Parkinson medication, (6-9) anticholinergic side effects i.e. blurred vision, urinating difficulty, constipation and dry mouth, (10) hypersalivation, (11) nausea, (12) dizziness, (13) getting tired quicker, (14) blunted affect/less need for companionship and lack of creativity, (15) menstrual disorder, (16-18) effectiveness; overall change in psychotic symptoms, depressive and cognitive symptoms, (19) routes of administration and (20) additional questions concerning patient characteristics such as smoking, history of epileptic convulsions, pregnancy wish.

In 2015 the United States Food and Drug Administration approved the partial dopamine agonists, cariprazine and brexpiprazole, for treatment of schizophrenia and as adjunctive for major depressive disorder.[7, 8] Subsequently, the European Medicine Agency (EMA) approved cariprazine in 2017 and brexpiprazole in 2018.[9, 10] The appearance of these agents on the Dutch market warrants an update to the PAC Index. Additionally, end-users observe that amisulpride is too often suggested as the most suitable option in the current index, seeming counterintuitive to clinicians' expectance. It is recommended that its ranking should be evaluated, especially considering new, potential higher-level, evidence published since its ranking in 2016.

We aim to evaluate and apply all evidence on cariprazine and brexpiprazole, and evidence post-2014 on amisulpride, to guide patients with non-affective psychosis in decision-making when choosing an antipsychotic agent using a specially designed algorithm. This evidence is integrated alongside updates to ranking of other agents when new data is available. We present an update of the online tool.

2. METHODS

To provide the most accurate update, the methods aim to replicate that of the tool's original development by *van Dijk et al*.

LITERATURE SEARCH

A syntax was devised per agent, categorized by intended and adverse effects (supplement 1). PubMed, EMBASE and the Cochrane Database were searched on March 7th, 2023, for meta-analyses, systematic reviews, and clinical trials. Rayyan[11] was used to screen on titles/abstract. Articles written in English or Dutch were included when the outcome was one of the previously defined intended or adverse effects of cariprazine, brexpiprazole or amisulpride, versus placebo or another agent. Studies were included when investigating non-affective psychosis (i.e., schizophrenia, schizoaffective disorder, schizophreniform disorder, and delusional disorder) in adults (>16 years) and excluded when only researching affective disorders (major depressive or bipolar disorder), drug-induced psychosis or psychosis 'not-otherwise-specified'. Further criteria warranting exclusion were augmented therapy (dual/combination therapy), unavailable full text, and exclusively pertaining to amisulpride; publications

<09/2014 (as they were evaluated by *van Dijk et al*).

References of articles were searched for additional publications. The Summary of Product Characteristics (SPCs) as provided by the EMA and pharmaceutical companies, National Institute of Mental Heath-Psychoactive Drug Screening Program (NIMH-PDSP) K_i Database[12] and Dutch pharmaceutical sources[13] were consulted.

2.2 Level of evidence

The eligible articles resulting from the search were ranked according to quality of evidence as follows:

a. Cochrane-reviews, (network)meta-analyses
b. Receptor occupancy profiles (values from the NIMH-PDSP K_i-database)
c. Randomized controlled trials (RCTs)
d. Laboratory studies
e. Summary of Product Characteristics (SPC)
f. Other public data in the Netherlands, e.g., *"het Farmacotherapeutisch Kompas"*, a prescription aid by the Dutch national health care institute.
g. Clinical experience of a panel of expert psychiatrists and researchers.

The results from the highest quality of evidence, assumed to be the best available data, were extracted. The K_i-database presents multiple values from different studies for one receptor. PDSP-Certified K_i-values are regarded as a higher level of confidence. If unavailable, an average is calculated from the results of human species.

2.3 Ranking

Van Dijk et al. created rankings based on effect sizes extracted from placebo-controlled studies and (network) meta-analyses.[6] The System of Objectified Judgement Analysis (SOJA)[14], was consulted to weigh the different items.

Agents with comparable effect sizes were categorized together, enabling allocation of agents without A-level evidence to a category when agent-to-agent comparisons suggested an equivalent effect size. The new agents were assigned to a category based on the same system of extracted effect sizes. If effect sizes were unavailable, the next best evidence was used (e.g., from systematic reviews or SPCs). Wherever new data was available, old rankings were updated in accordance, potentially leading to newly defined cut-offs for the categories. The cut-offs were aided by receptor-affinities and/or D- to G-level data.

2.4 Algorithm

The weight of the item is proportional to the rank. An agent in category 2 out of 4, weighs 0.50. Agents with insufficient/ambiguous data will usually weigh the mean for that item. The PAC-index respondent indicates relevance on a scale from 0 (very unacceptable) to 4 (very acceptable). The proportional rank is multiplied by the assigned relevance. All side-effects are summed up and multiplied by -1. Effectiveness weights are multiplied by 4 (overall and depressive) or 2 (cognition) to emphasise the importance of effectiveness. Figure 1 shows a schematic representation of the algorithm weights.

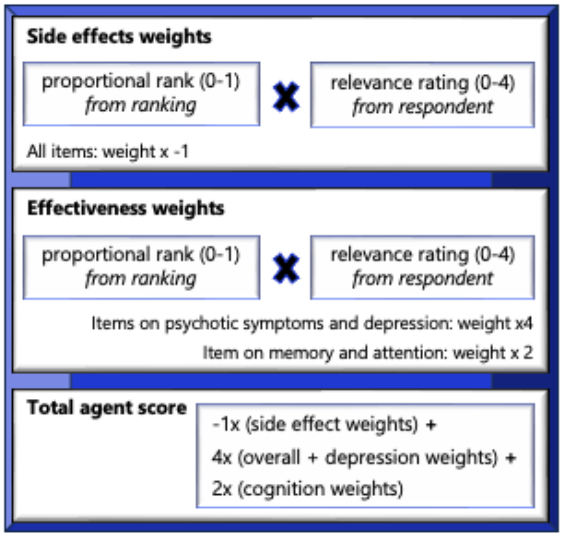

Figure 1. schematic overview of algorithm scoring

2.5 Panel

To test the clinical accuracy of the rankings, a panel of clinicians, identical to the original development, were invited to review the updated tables. Adjustments based on expert feedback are shown by the respective categories.

3. Results

3.1 Article selection

For cariprazine, brexpiprazole and amisulpride, respectively 391, 224 and 406 articles were found after an initial search. Of those 65, 46 and 54 remained eligible after title/abstract screening. Flowcharts are found in the appendix (supplement 2_{1-3}). After ranking according to level of evidence (supplement 3), the data was extracted from the best available evidence, shown below.

Table 1. Included Articles

Cochrane reviews & (Network) Meta-analyses	Pillinger et al. 2020[15]	18 incl. CAR, BRE, AMI	Metabolic parameters, weight gain	2-13, median 6 weeks	No exclusion of treatment resistance, first episodes or predominant NS.
	Huhn et al. 2019[16]	32 incl. CAR, BRE, AMI	Effectiveness: overall, negative, positive, depressive, social functioning Side effects: weight gain, EPS, prolactin change, sedation, anticholinergic effects	3-13, primary point 6 weeks (mean 7 weeks)	Exclusion: first episode, treatment resistance, predominant negative symptoms, major concomitant somatic/psychiatric illness.
	Leucht et al. 2017[17]	25 incl. CAR, BRE	Effectiveness: positive, negative, quality of life, social functioning Side effects: weight gain, EPS, prolactin, sedation	3-28, median 6 weeks	Exclusion: predominant negative symptoms, major concomitant somatic/psychiatric illness
RCT	Fleisschhacker et al. 2019[18]	CAR vs. RIS	Cognition	26 weeks	Inclusion: persistent/predominant negative symptoms

CAR: cariprazine, BRE: brexpiprazole, AMI: amisulpride, RIS: risperidone, EPS: extrapyramidal side-effects

3.2 RANKING AGENTS

TABLE 2. WEIGHT GAIN

Cat.	Agent. effect size, (CI)	Source
3	clozapine **MD* 3.01**	**Pillinger et al.**[15]
	olanzapine **MD 2.73**	
2	quetiapine **MD 1.56**	**Pillinger et al.**[15]
	risperidone **MD 1.28**	
1	**brexpiprazole MD 0.88**	**Pillinger et al.**[15]
	flupentixol **MD 0.75**	**Pillinger et al.**[15]
	cariprazine MD 0.66	**Pillinger et al.**[15]
	amisulpride MD 0.66	**Pillinger et al.**[15]
	zuclopenthixol **MD 0.53**	**Huhn et al.**[16]
	sulpiride	Kumar et al.[19] (equals zuclopenthixol)
	aripiprazole **MD 0.34**	**Pillinger et al.**[15]
	lurasidone **MD 0.32**	**Pillinger et al.**[15]
	haloperidol **MD -0.23**	**Pillinger et al.**[15]
	pimozide	Mothi et al.[20] (equals placebo)
***	perphenazine **10%****	Strassnig et al.[21]
	penfluridol	SPC: mentioned without indicating prevalence
	pipamperone	no data

*Cat.: category; *MD: mean difference compared to placebo; ** gained >7% weight, n =14; 3: strongest effect; ***: ambiguous/ insufficient data.*

Both meta-analyses by *Huhn et al.* and *Pillinger et al.* examined weight gain. Inclusion criteria used by *Pillinger et al.* are tailored to investigate metabolic changes, including studies with comorbid diseases and potential modifiers of metabolic parameters, and evaluates whether these were similarly distributed amongst groups. Hence, this data was chosen to incorporate the new agents in the ranking. The other available agents were also updated based on MD's reported by *Pillinger et al.*, as opposed to the standardized mean differences used by *van Dijk et al.* Only zuclopenthixol was not reported on by *Pillinger et al.* so data from *Huhn et al.* is used as next best. Sulpiride was assigned category 1 due to the Cochrane review on zuclopenthixol in which *Kumar et al.* report equality between the two. The cut-offs are an MD > 2 for category 3, >1 for category 2, and MD < 1 was assigned category 1.

Algorithm

Agents with ambiguous/insufficient data are assigned the mean weight of the item (2).

TABLE 3. SEXUAL DYSFUNCTION

Cat.	Agent. effect size, (CI)	Source
4	**amisulpride SMD* 1.38 (0.73, 2.02)**	**Huhn et al.[16] (supplements)**
	sulpiride	Peuskens e.a.[22] [comparable to amisulpride]
	risperidone **SMD 1.17 (1.03, 1.3)**	**Huhn et al.[16] (supplements)**
3	haloperidol **SMD 0.71 (0.58, 0.85)**	**Huhn et al.[16] (supplements)**
	perphenazine	Peuskens et al.[22] [comparable to haloperidol (as FGA)]
	pipamperone	
	zuclopentixol	
	pimozide	
	flupentixol **SMD 0.5 (-0.18, 1.19)**	**Huhn et al.[16] (supplements)**
2	lurasidone **SMD 0.28 (0.09, 0.48)**	
	olanzapine **SMD 0.15 (0.02, 0.28)**	**Huhn et al.[16] (supplements)**
	brexpiprazole SMD 0.13 (-0.11, 0.36)	
1	**cariprazine SMD -0.1 (-0.37, 0.18)**	**Huhn et al.[16] (supplements)**
	quetiapine **SMD -0.13 (-0.29, 0.04)**	**Huhn et al.[16] (supplements)+** Gardner et al.[23] [comparable to aripiprazole]
	aripiprazole **SMD -0.22 (-0.39, -0.05)**	**Huhn et al.[16] (supplements)**
	clozapine **SMD -2.05 (-3.6, -0.5)**	**Huhn et al.[16] (supplements)+** Haddad et al.[24] [comparable to quetiapine]
**	penfluridol	

*Cat.: category; *SMD: standard mean difference compared to placebo; negative values indicate that the antipsychotic agent is favoured over placebo; **insufficient/ambiguous data; FGA: first generation antipsychotics; 4 = strongest effect*

An important factor in sexual dysfunction is hyperprolactinemia[25]. Data was extracted from *Huhn et al.* to rank the new agents. An SMD was available for many of the other previously incorporated agents and their ranking was therefore updated accordingly. The cut-off for category 4 is SMD > 1, category 3 is SMD > 0,5, category 2 is SMD > 0 and category 1 corresponds to SMD < 0. No data, or data of poor quality was available for perphenazine, pipamperone, zuclopenthixol and pimozide, thus using the original ranking based on comparability to haloperidol.

Algorithm

Agents with ambiguous/insufficient data are assigned the mean weight of the item (2).

TABLE 4. MENSTRUAL DISORDER

Identical ranking to table 3, sexual dysfunction, based on similar pathophysiology of hyperprolactinemia.

TABLE 5. DROWSINESS (SEDATION)

Cat.	Agent. effect size, (CI)	Source
4	sulpiride **RR* 4.08 (2.04, 10.10)**	**Huhn et al.[16]**
	quetiapine **RR 3.27 (2.61, 4.22)**	**Huhn et al.[16]**
	clozapine **RR 3.02 (2.52, 3.37)**	**Huhn et al.[16]**
	perphenazine **RR 1.09 (0.31, 2.09)**	**Huhn et al.[16]** RR counterintuitive to expert opinion/H_1-affinity 8, comparable to quetiapine (10)[12]
3	olanzapine **RR 2.17, (1.93, 2.40)**	**Huhn et al.[16]**
	risperidone **RR 2.03 (1.67, 2.51)**	**Huhn et al.[16]** + Muench et al.[26] [comparable to haloperidol]
	haloperidol **RR 1.92 (2.27, 2.90)**	**Huhn et al.[16]**
	pipamperone **no RR**	H_1- affinity 2400, comparable to haloperidol (3002)[12]
	pimozide **RR** 0.92 (0.17, 2.03)**	**Huhn et al.[16]** LoE very low (n=30). H_1-affinity 359, comparable to haloperidol (3002)[12] **
	zuclopenthixol **RR 10.20 (4.72, 29.41)**	Huhn et al.[16] LoE low (n=76). H_1-affinity unknown. Kumar et al.[19] > placebo
2	lurasidone **RR 1.75 (1.38, 2.11)**	**Huhn et al.[16]**
	brexpiprazole RR 1.64 (0.91, 2.38)	
	amisulpride RR 1.56 (0.91, 2.23)	
	aripiprazole **RR 1.46 (1.11, 1.83)**	
1	penfluridol **RR 1.24(0.53, 2.04)**	**Huhn et al.[16]**
	flupentixol **RR 1.12 (0.70, 1.59)**	
	cariprazine RR 1.12 (0.70, 1.59)	

*Cat.: category; * RR: relative risk compared to placebo; **ranked according to comparability to haloperidol due to low LoE: level of evidence.*

Huhn et al. report an RR for cariprazine, brexpiprazole and amisulpride, plus the previously included agents except pipamperone (for which an effect size was originally unavailable as well). All available agents have been updated from odds ratio and number needed to harm (original ranking) to RR. Cut-offs are based on the RR. In case of doubt (i.e. poor level of evidence[LoE]), guided by histamine-receptor (H_1) blockage, a mechanism which antipsychotic-related sedation relies strongly on.[27] A rounded RR of > 3.0 is assigned to category 4, RR > 2.0 to category 3, RR > 1.5 to category 2, and < 1.5 to category 1. Pipamperone and pimozide are ranked with haloperidol according to similar H_1-affinity. Despite available RR, pimozide's very LoE and zuclopenthixol's considerable confidence interval (CI) a critical, multifactorial ranking is necessary.

Expert panel

In clinical practice, perphenazine seems to be more sedative than the RR suggests. The ranking has been adjusted based on H_1-receptor affinity.

TABLE 6. SLEEP

Identical ranking to table 5, drowsiness, based on similar pathophysiology of sedation and H_1-receptor blockage.

TABLE 7. EXTRAPYRAMIDAL SIDE EFFECTS

Cat.	Agent. effect size, (CI)	Source
3	pimozide **RR* 5.14 (4.81, 6.55)**	**Huhn et al.[16]**
	flupentixol **RR 3.9 (1.27, 5.65)**	**Huhn et al.[16]**
	penfluridol **RR 3.48 (1.21, 5.12)**	**Huhn et al.[16],** SPC: comparable to haloperidol
	haloperidol **RR 3.13 (2.74, 3.50)**	**Huhn et al.[16]**
	zuclopenthixol **RR 3.06 (1.60, 6.90)**	**Huhn et al.[16],** SPC: comparable to haloperidol
2	perphenazine **RR 2.64 (1.32, 3.92)**	**Huhn et al.[16]**
	sulpiride **RR 2.38. (1.07, 7.35)**	**Huhn et al.[16] very low LoE****
	cariprazine RR 2.21 (1.18, 3.98)	**Huhn et al.[16], very low LoE**
1	lurasidone **RR 1.94 (1.42, 2.48)**	**Huhn et al.[16]**
	risperidone **RR 1.80 (1.40, 2.38)**	**Huhn et al.[16]**
	pipamperone -	Schillevoort et al.[28], [comparable to risperidone]
	brexpiprazole RR 1.60 (0.80, 2.63)	**Huhn et al.[16]**
	amisulpride RR 1.46 (0.96, 2.04)	**Huhn et al.[16]**
	aripiprazole **RR 1.32 (0.90, 1.82)**	**Huhn et al.[16]**
	quetiapine **RR 1.05 (0.78, 1.48)**	**Huhn et al.[16]**
	olanzapine **RR 1.02 (0.79, 1.30)**	**Huhn et al.[16]**
0	clozapine **RR 0.46 (0.19, 0.88)**	**Huhn et al.[16]**

*Cat.: category; * RR: odds ratio compared to placebo; ** LoE: level of evidence, unspecified = low; 0 = protective effect, 3 = strongest effect*

Originally, *van Dijk et al.* extracted data from the meta-analysis of *Leucht et al. (2013)*[29] in which EPS was measured by use of anti-Parkinson medication and D_2-receptor affinity. The same measure is applied. The number of categories is reduced from 6 to 4 to decrease the algorithm weight, regarding the low LoE. Categories coincide with round numbers for RR (>3, <3, <3 and <1 per decreasing category, respectively). RR for pipamperone is unavailable, ranking is based on similarities to risperidone (as done originally by *van Dijk et al.*)

Algorithm

Clozapine, in category 0, is a protective factor in EPS. Its weight in the algorithm should be 0 to signify no risk of EPS.

TABLE 8. ANTICHOLINERGIC EFFECTS

Cat.	Agent. effect size, (CI)	Source
3	quetiapine **RR* 3.89**	**Huhn et al.[16] moderate LoE ****
2	clozapine **RR 2.21**	**Huhn et al.[16] very low LoE**
	olanzapine **RR 1.94**	**Huhn et al.[16], moderate LoE**
1	penfluridol **RR 1.63 (0.51, 3.56)**	**Huhn et al.[16], very low LoE**
	amisulpride RR 1.53 (0.75, 2.66)	**Huhn et al.[16],** M_1 affinity > 10.000 (unchanged).
	haloperidol **RR 1.50 (1.14, 1.93)**	**Huhn et al.[16],** M_1 affinity 10.000
	cariprazine RR 1.45	**Huhn et al.[16], very low LoE,** SPC: **"**no appreciable affinity for cholinergic muscarinic receptors".
	perphenazine **RR 1.32 (0.58, 2.48)**	**Huhn et al.[16],** M_1 affinity 1496[12]
	risperidone **RR 1.31 (1.03, 1.72)**	**Huhn et al.[16],** dose-AA relation: zero. M_1 affinity 10.000[12]
	aripiprazole **RR 1.30 (0.83, 1.90)**	**Huhn et al.[16],** dose-AA relation: zero. M_1 affinity 6778[12]
	pimozide **RR 1.17 (0.40, 2.49)**	**Huhn et al.[16], very low LoE,** M_1 affinity 800[12]
	lurasidone **RR 1.14**	**Huhn et al.[16],** M_1 affinity > 1000[12]
	sulpiride **RR 1.01 (0.47, 2.86)**	**Huhn et al.[16], very low LoE**
	pipamperone no RR	Comparable to haloperidol in M_1 -receptor affinity
0	**brexpiprazole RR 0.72**	**Huhn et al.[16],** No known affinities. No side effects mentioned in SPC.
***	zuclopenthixol **RR 2.73 (0.81, 23.26)**	**Huhn et al.[16]**
	flupentixol **RR 2.14**	**Huhn et al.[16], very low confidence**

*Cat.: category; *RR: relative risk compared to placebo; ** LoE: level of evidence, unspecified = low; 3 = strongest effect.*

Huhn et al. define anticholinergic side-effects as at least one of the following symptoms: blurred vision, constipation, dry mouth/hyposalivation or urinary retention, corresponding to the PAC-Index items. Previously, muscarinic receptor affinity was used to estimate propensity for anticholinergic side effects, as no effect sizes were available. *Huhn et al.* report an RR for most of the agents, allowing an elaborate update. Cut-offs are aided by M_1-affinities and SPCs. Quetiapine is assigned its own category considering the significantly higher RR, followed by a round RR < 3 for category 2, RR < 2 for category 1 and < 1 for category, 0, favoring the agent over placebo. Anticholinergic side-effects are rare for the agents ranked in category 1. Only pipamperone has no available RR, remaining in category 1 due to its similarity to haloperidol.

Expert panel

Zuclopenthixol and flupentixol have a substantial CI/low LoE making ranking based on RR unreliable. Additionally, it seems counterintuitive to expert opinion. Therefore, they are assigned to insufficient/ambiguous evidence.

Algorithm

The insufficient/ambiguous evidence category is assigned the mean weight of 1.5.

TABLE 9. HYPERSALIVATION

Cat.	Agent. prevalence, (CI)	Source
4	clozapine 32.7 % * (29–37)	Ozbilen et al.[30] 16, n = 559
3	zuclopenthixol 24.2 % (16–36)	Ozbilen et al.[30] 2, n=53
2	haloperidol 18.4 % (16–21)	Ozbilen et al.[30] 12, n = 1115
	amisulpride 7.8 % (4–14)	Ozbilen et al.[30] 5, n = 115. **SPC: very common (>10%)**
1	olanzapine 8.2 % (7–10)	Ozbilen et al.[30] 5, n = 1857
	cariprazine <10%, >1%	**SPC: common**
	brexpiprazole <10%, >1%	
	risperidone 5.7 (2–6)	Ozbilen et al.[30] 3, n = 325
**	penfluridol	No data
	flupentixol	
	aripiprazole	
	lurasidone	
	sulpiride	
	perphenazine	
	pipamperone	
	quetiapine	
	pimozide	

*Cat.: category; *prevalence (standard deviation); ** ranked #2 (mean weight) because of insufficient information*

No effect size was found for cariprazine or brexpiprazole, prevalence statistics were obtained from the SPCs.

Amisulpride's SPC mentions hypersalivation as 'very common'. Although no source is stated, the latest update was very recent, on the 12th of January 2023. The value on which it was previously ranked (7.8%) is obtained from one RCT from 1996 with a sample size of 115. The SPC was regarded as more reliable and amisulpride was moved to category 3.

Van Dijk et al. extracted prevalence from a systematic review of Cochrane reviews by *Ozbilen et al.*[30] and categorized risperidone solitary in category 1. It is now joined by olanzapine, cariprazine and brexpiprazole, sharing a prevalence of <10%. Category 2 corresponds to a prevalence > 10%, 3 to > 20% and 4 > 30%.

Algorithm

Agents with insufficient data were categorized as ** and given the mean weight of the item (2).

TABLE 10. NAUSEA

Cat.	Agent	Source
2	aripiprazole	
	clozapine	
	cariprazine	
	olanzapine	SPC: "common"
	pimozide	
	lurasidone	
	amisulpride	
1	**brexpiprazole**	**SPC: "uncommon"**
*	sulpiride	SPC: "unknown"
	quetiapine	
	risperidone	
	haloperidol	
	pipamperone	
	zuclopenthixol	
	flupentixol	
	perphenazine	
	penfluridol	

*Cat.: category; *ranked #2 (mean weight) due to insufficient information; 3 = strongest effect; ARI: aripiprazole; QUE: quetiapine; RIS: risperidone; CLO: clozapine*

The mechanism of nausea due to antipsychotic use is unclear, and in practice often multifactorial and complex. *Fitzsimons*[31] suggested delayed gastric emptying due to anticholinergic effects, or increased appetite due to hypersalivation could play a role in clozapine-use. It remains speculation, making it difficult to rely on receptor affinities. Despite these difficulties, patient panels regard this item as important therefore warranting a place in the algorithm. Consequently, the ranking uses SPC information. Brexpiprazole was assigned its own category, as the only agent for which nausea is uncommon.

Algorithm

Agents with insufficient data were given a weight of 1.5, in between "uncommon" and "common", to not over- or underestimate the effect.

TABLE 11. DIZZINESS

Category	Agent	Source
3	clozapine	α1-receptor affinity **1.6[12] SPC: very common**
2	risperidone	α1-receptor affinity **5[12]**, **SPC: common**
	perphenazine	α1-receptor affinity 10[12], **SPC: common**
	haloperidol	α1-receptor affinity **12[12], SPC: common**
	quetiapine	α1-receptor affinity **22[12]****
	brexpiprazole	**α1-receptor affinity 24[12], SPC: common**
	aripiprazole	α1-receptor affinity **25[12]**
1	lurasidone	α1-receptor affinity **47[12]**
	pipamperone	**α1-receptor affinity 66[12]***
	olanzapine	A1-receptor affinity **109[12]**; **SPC: common**
	pimozide	α1-receptor affinity 138[12]*
	cariprazine	**α1-receptor affinity > 379[12], SPC: common**
0	**amisulpride**	**α1-receptor affinity > 10,000[12], SPC: no mention**
	sulpiride	**α1-receptor affinity > 10,000[12]***
*	penfluridol	
	flupentixol	No data
	zuclopenthixol	

**ranked mean weight (#2) due to insufficient information; **not PDSP certified; 3 = strongest effect*

Van Dijk et al. ranked the agents according to their adrenergic α1-receptor affinity due to the heterogeneity and ambiguity in outcomes of clinical data from Cochrane Reviews and others[32, 33]. The α1-receptor, A-subtype is involved in regulating orthostatic hypotension, the mechanism in which dizziness manifests with i.e., clozapine[34] and olanzapine. Its affinity values were extracted to add cariprazine and brexpiprazole. Due to new, more reliable affinity data, many other agents were updated as well. For pipamperone, only a value from rat cortex was available.

A Cochrane Review by *Duggan et al.*[52] from 2005 demonstrated significantly less dizziness with olanzapine than FGA (first-generation antipsychotics) after two years of treatment (RR = 0.51). Therefore, olanzapine's α1-receptor affinity, aided by information from SPCs, are used for cut-off assessments. Clozapine was ranked in its own category based on its very strong affinity, reinforced by information from its SPC. K_i-values between 5-25 were ranked category 2 and > 25 ranked category 1. Amisulpride and sulpiride were ranked in category 0, as they do not cause dizziness. Penfluridol, flupentixol and zuclopenthixol are assigned to the *-category due to no data available.

Algorithm

Agents with insufficient data were given the mean weight of the item (2).

TABLE 12. GET TIRED QUICKER

Cat.	Agent	Source
2	clozapine	
	olanzapine	
	quetiapine	
	pimozide	
	perphenazine	
	risperidone	
	haloperidol	Schillevoort et al.[28]
	penfluridol	
	flupentixol	
	sulpiride	
	pipamperone	
	lurasidone	
	zuclopenthixol	
	amisulpride	SPC: somnolence common
	cariprazine	**SPC: fatigue "common"**
	brexpiprazole	**SPC: fatigue "common"**
1	aripiprazole	Schillevoort et al.[28]

Cat.: category; 2 = strongest effect on fatigue

No effect sizes were found regarding fatigue. SPC's were used to rank cariprazine and brexpiprazole in category 2. Amisulpride's SPC does not mention fatigue, however somnolence is reported as common adverse effect, meriting a category 2 ranking.

Van Dijk et al. found fatigue to be very under-researched. The rest of the ranking is based on the only available evidence, a Cochrane review by *Schillevoort et al.*[28], reporting a trend favoring aripiprazole over other SGA (second-generation antipsychotics). Aripiprazole is ranked in its own category, with the least likelihood to cause fatigue. All other agents were placed in category 2.

TABLE 13. BLUNTED AFFECT/LESS NEED FOR COMPANIONSHIP/LESS CREATIVITY

Cat.	Agent	Source
2	perphenazine	D_2 affinity 1[12]*
	lurasidone	D_2 affinity 1.7[12]*
	haloperidol	D_2 affinity **2**[12]
	risperidon	D_2 affinity **4.9**[12]
	penfluridol	chemical compounds similar to haloperidol, D_2 affinity 5.6* (calf 1976)[12]
	zuclopenthixol	chemical compounds similar to haloperidol, no known affinities
	pimozide	D_2 affinity **6**[12]* affinity similar to haloperidol
	pipamperone	chemical compounds similar to haloperidol, D_2 affinity 7[12]*
	sulpiride	D_2 affinity **8**[12]*
1	**cariprazine**	D_2 **affinity 18**[12]
	brexpiprazole	D_2 **affinity 40**[12]
	olanzapine	D_2 affinity **72**[12]
	clozapine	D_2 affinity **431**[12]
	quetiapine	D_2 affinity **567**[12]
	amisulpride	D_2 **affinity 2,407**[12]
	aripiprazole	D_2 affinity 0.95[12]; partial agonism

*Cat.; category; 2 = strongest effect on blunted affect/need of companionship; * not PDSP certified*

Blunted affect is under-researched in RCT's. *Van Dijk et al.* assessed blunted affect/less need for companionship as subjective well-being, which is correlated to non-linear D_2-receptor binding. Less binding triggers more psychotic symptoms and reduced motivation, while higher occupancy causes less reward stimuli and flattened emotions. *De Haan*[36] establishes an optimal D_2-occupancy at 60-70%. Thus, agents are ranked according to their D_2-affinity being similar/less than that of dopamine (1.5nM), and agonism of dopaminergic neurotransmission. *Leucht et al.*[17] assessed quality of life (6 studies) and social functioning (10 studies), and *Huhn et al.*[16] evaluates social functioning (16 studies), all with heterogenous results. Hence, we rely on D_2-affinities for the two new agents and K_i-values are updated to PDSP-certified.[12]

TABLE 18. EPILEPTIC SEIZURE

Cat.	Agent. incidence, (CI)	Source
4	clozapine SIR* 9.5/9.00%**	Alper et al.[37]/Kumlien et al.[38]
3	quetiapine SIR 2.50/5.90 % olanzapine SIR 2.05/4.91 %	Alper et al.[37]/Kumlien et al.[38]
2	zuclopenthixol 4.18 %	Kumlien et al.[38]
	risperidone 3.68 %	Alper et al.[37]/Kumlien et al.[38]
	pimozide 3.40 %	Lertxtundi et al.[39]; SPC: caution, "grand-malconvulsions reported"
	haloperidol 3.27 %	Kumlien et al.[38]
	perphenazine 3.19 %	Kumlien et al.[38] SPC: extra caution, is a phenothiazine
	flupentixol 2.58 %	Kumlien et al.[38]
	aripiprazole 2.59 %	Kumlien et al.[38]
1	sulpiride 0.5 %	Lertxtundi et al.[39]
***	pipamperone	No data
	amisulpride	**SPC: "uncommon", "may lower seizure threshold"**
	lurasidone	SPC: "use cautiously", no further data
	cariprazine	**SPC: "rare", "use cautiously"**
	brexpiprazole	**SPC: "unknown", "use cautiously"**
	penfluridol	

*Cat.: category; *standardised incidence ratio; ** % convulsions of total no. of adverse drug reactions; *** no or ambiguous data, ranked mean weight (#2)*

Van Dijk et al. used incidence to achieve the original ranking. Since, no new publications describe seizure incidence. SPCs were used to rank amisulpride, cariprazine and brexpiprazole. The SPCs of amisulpride and cariprazine report uncommon and rare occurrences of seizures, though advise cautious use. The agents are therefore assigned in the ambiguous category.

The rest of the ranking remains original, based 3 studies. *Alper et al.*[37] retrieved standardized incidence ratios for seizure from phase II and III trials of Basis of Approval Reports USA, where only clozapine, quetiapine and olanzapine showed significantly higher ratios. *Kumlien et al.*[38] and *Lertxundi et al.*[39] used drug reaction databases of the World Health Organization and Spain (Basque country), respectively, to determine the percentage of insults on total spontaneously reported adverse drug events per antipsychotic agent. Despite the high risk of bias, this data was the best available evidence for incidence. Due to the larger dataset of *Kumlien et al.* and similarity to *Alper et al.*, its results were regarded as more important.

Algorithm

Agents in the ambiguous category are assigned the mean item weight (2).

TABLE 14. EFFECTIVENESS: OVERALL CHANGE IN PSYCHOTIC SYMPTOMS

Cat.	Agent. effect size, (CI)	Source
4	clozapine **SMD* -0.89 (-1.08, -0.71**)	**Huhn et al.[16]**
	amisulpride SMD -0.73 (-0.89, -0.58)	**Huhn et al.[16] moderate LoE**
3	olanzapine **SMD -0.56 (-0.62, -0.50)**	**Huhn et al.[16] moderate LoE**
	perphenazine SMD -0.56	**Huhn et al.[16] moderate LoE**
	risperidone **SMD -0.55 (-0.62, -0.48)**	**Huhn et al.[16] high LoE**
2	zuclopenthixol **SMD -0.51 (-0.72, -0.27)**	**Huhn et al.[16]**
	sulpiride **SMD -0.48 (-0.87, -0.09)**	**Huhn et al.[16]**
	haloperidol **SMD -0.47 (-0.53, -0.41)**	**Huhn et al.[16] moderate LoE**
	quetiapine **SMD -0.42 (-0.50, -0.32)**	**Huhn et al.[16] moderate LoE**
	aripiprazole **SMD -0.41 (-0.52, -0.30)**	**Huhn et al.[16]**
1	penfluridol **SMD -0.39 (-0.52, -0.26)**	**Huhn et al.[16] very low LoE**
	lurasidone **SMD -0.36 (-0.48, -0.24)**	**Huhn et al.[16]**
	cariprazine SMD -0.34 (-0.49, -0.20)	**Huhn et al.[16] very low LoE**
	pimozide **SMD -0.30 (-0.75, 0.14)**	**Huhn et al.[16] very low LoE**
	brexpiprazole SMD -0.26 (-0.39, -0.12)	**Huhn et al.[16] very low LoE**
	flupentixol **SMD -0.24 (-0.53, 0.05)**	**Huhn et al.[16] very low LoE**
***	pipamperone	

*Cat.: category; *standard mean difference compared to placebo; **LoE: level of confidence in evidence, unspecified = low; 4 = strongest effect*

Data from *Huhn et al.* was extracted to add new agents cariprazine, brexpiprazole and evaluate amisulpride. New data was available for most other agents as well, including flupentixol, sulpiride and zuclopenthixol (previously no SMD), which allowed for an update of the entire table.

Amisulpride joined clozapine in the highest category, 4, as its effect size (<-0.70) is significantly greater than olanzapine, the next greatest (category 3, >-0.60). Agents with an SMD between -0.40 and -0.50 ranked in category 2. The agents with the lowest LoE were also the agents with the least effectiveness, <-0.40, ranking in category 1. Although penfluridol's SMD lies closer to aripiprazole than lurasidone, penfluridol is included in category 1 to prevent overestimating its effectiveness on account of the low LoE. No clear evidence was found for pipamperone, therefore it is assigned to the ***-category, as originally done by *van Dijk et al.*

Algorithm

Van Dijk et al. previously assigned clozapine an algorithm weight of 18, 6 for the following category (olanzapine and amisulpride) and 5 the remaining category. The ambiguous category is assigned the weight of the weakest category.

TABLE 15. EFFECTIVENESS: DEPRESSIVE SYMPTOMS

Cat.	Agent. effect size, (CI)	Source
4	sulpiride **SMD* –0.90 (-1.36, -0.44)**	**Huhn et al.[16] n=52**
	clozapine **SMD -0.52 (-0.82, -0.23)**	**Huhn et al.[16] low LoE ****
3	**amisulpride SMD -0.44 (-0.60, -0.28)**	**Huhn et al.[16] high LoE**
	aripiprazole **SMD -0.40 (-0.69, -0.10)**	**Huhn et al.[16]**
	olanzapine **SMD -0.37 (-0.46, -0.29)**	**Huhn et al.[16] high LoE**
	cariprazine SMD -0.36 (-0.63, -0.09)	**Huhn et al.[16]**
2	quetiapine **SMD -0.24(-0.34, -0.11)**	**Huhn et al.[16] high LoE**
	risperidone **SMD -0.23 (-0.34, -0.11)**	**Huhn et al.[16]**
	lurasidone **SMD -0.20 (-0.32, -0.09)**	**Huhn et al.[16] low LoE**
	pimozide **SMD -0.20 (-0.87, 0.46)**	**Huhn et al.[16] low LoE, n=20**
1	penfluridol **SMD -0.18 (-0.94, 0.60)**	**Huhn et al.[16] low LoE, n=14**
	haloperidol **SMD -0.17 (-0.26, -0.08)**	**Huhn et al.[16]**
	brexpiprazole SMD -0.16 (-0.53, 0.20)	**Huhn et al.[16]**
	zuclopenthixol **SMD -0.16 (-0.29, -0.03)**	**Huhn et al.[16]**
0	flupentixol **SMD 0.04 (-0.39, 0.47)**	**Huhn et al.[16]**
***	perphenazine	SPC: antidepressant (MAO-I)

*Cat.: category; *standard mean difference compared to placebo; **LoE: level of confidence in evidence, unspecified = moderate; ***ambiguous/insufficient data; 4 = strongest effect*

Again, data from *Huhn et al.* was extracted to add new agents cariprazine, brexpiprazole and evaluate amisulpride. *Huhn et al.* reported SMDs for all agents except perphenazine. This allowed for an elaborate update to the entire table, previously based on Hedge's g from *Leucht et al.*[29]

Category 4 contains the agents with an effect size < -0.50. Sulpiride was not given its own category due to the large CI and low sample size of this criterion. Category 3 corresponds to SMD <-0.30, category 2 to SMD <-0.20 and category 1 to SMD <-0.10. Flupentixol was assigned its own category at 0. Perphenazine was previously ranked in the ambiguous category based on SPC information. In the latest update, May 16th, 2022, there is no mention of adverse effect on depression though a risk of worsening of suicidal tendencies is described, especially for adolescents under 25 years old. Additionally, perphenazine is a MAO-inhibitor of which effectiveness is described for depression.

Algorithm

Perphenazine is given the mean weight of the item (2).

TABLE 16. EFFECTIVENESS: MEMORY AND ATTENTION PROBLEMS

Category	Agent. effect size, (CI)	Source
1	olanzapine MDes* -0.27	Désaméricq et al.[40]
	quetiapine MDes -0.20	Désaméricq et al.[40]
	cariprazine LSMD ** -0.15 in G11 category	**Fleisschhacker et al.[18] CAR>RIS**
****	**brexpiprazole**	Désaméricq et al.[40]
	haloperidol	
	amisulpride	
	risperidone MDes NS***	
	flupentixol	
	perphenazine	
	penfluridol	
	zuclopentixol	
	pimozide	
	pipamperone aripiprazole	
	clozapine	
	sulpiride	
	lurasidone	

**MDes: mean different effect size compared to haloperidol and amisulpride; **LSMD: least squares mean difference; effect size compared to risperidone; ***NS: no significant difference in effect size compared to haloperidol and amisulpride; ****ambiguous/insufficient data; 1 = probably favorable effect.*

For the ranking of cariprazine, we used a study by *Fleischhacker et al.*[18] This post-hoc analysis evaluates subcategories of the Positive and Negative Syndrome Scale (PANSS). In the G11 subcategory concerning attention, cariprazine is favoured over risperidone with an LSMD of -0.15.

Another study by *Fleischhacker, et al.*[41] regards brexpiprazole, showing improvement on cognition as measured with the Cogstate Brief Battery test, with an MD of 0.19 compared to placebo (Cohen's d = 0.298 signifying a medium-small effect size). Despite a reasonable sample- and effect size, lack of specificity in cognitive domains plus the lack of agent-to-agent comparison makes this result ambiguous. We ranked brexpiprazol in the 'ambiguous/no data' category.

For amisulpride, two new meta-analyses were found (*Nielsen et al.* 2015[42] and *Baldez et al.* 2021[43]). Both include the open-label study (*Davidson et al.* 2009[44]) on which *Désaméricq et al.* based his data, as well as an additional two[45, 46]. Due to the small sample sizes (11 and 18) the results of these meta-analyses are regarded as too ambiguous and amisulpride remained in its category.

Algorithm

Agents in the ambiguous category are assigned the mean item weight (0.5).

TABLE 17. ROUTES OF ADMINISTRATION

Cat.	Agent	Source
1	quetiapine	Farmacotherapeutisch
	clozapine	Kompas
	perphenazine	
	amisulpride	
	pimozide	
	aripiprazole	
	pipamperone	
	flupentixol	
	sulpiride	
	lurasidone	
	cariprazine	
	brexpiprazole	
2	penfluridol	
3	zuclopenthixol	
	haloperidol	
	pipamperone	
	sulpiride	
4	haloperidol	
	olanzapine	
	risperidone	
	perphenazine	
	zuclopenthixol	
	aripiprazole	
	flupentixol	

*Cat.: category; *(1) tablets daily, (2) 1-2 tablets per week, (3) fluid administration daily, and (4) depot injections.*

Brexpiprazole and cariprazine have been added.

Algorithm

NB: not all agents are listed in category 1 to supply the algorithm with the correct information.

3.3 PANEL

The rankings were reviewed by IS, JV, MK and JZ, resulting in amendments to drowsiness and anticholinergic effects rankings, of which details are incorporated in the respective categories. Suggestions were made to combine drowsiness, sleep and getting tired quicker, and to eliminate nausea and memory and attention problems because of its complex and multifactorial nature. These items were selected by patient panels and individually regarded as important, so they must remain incorporated.

4. DISCUSSION

We incorporated evidence on brexpiprazole, cariprazine and amisulpride to update the PAC-index. Mainly two network meta-analyses were used, *Pillinger et al.*[15] and *Huhn et al.*[16], aided by a clinical panel. Data was extracted and ranked compliant with the process developed by *van Dijk et al.*,[6] allowing an elaborate update to this decision-making tool, while maintaining its transparent quality to facilitate future updates.

Cariprazine and brexpiprazole tend to rank favourably on adverse effects, although lower on effectiveness, bar cariprazine for depressive symptoms. Amisulpride improved ranking on

effectiveness, EPS, nausea, dizziness, and affect, and deteriorated in prolactin, sedation, anticholinergic effects and hypersalivation. Table 1 of the appendix (supplement 5) provides a summary with comparisons to the original rankings.

The evidence on the new agents required major ranking updates for sedation, anticholinergic effects and depressive symptoms, and minor changes in EPS, hypersalivation, dizziness, and effectiveness. Drowsiness, originally based on receptor affinity, was updated due to availability of effect sizes. Effect sizes were still lacking for hypersalivation, nausea, dizziness, tiredness, blunted affect, and effectiveness on memory and attention. New data for weight gain, prolactin, nausea, getting tired quicker, blunted affect, insults, and memory and attention did not change rankings.

Sexual health and menstrual disorders were measured by hyperprolactinemia. Prolactin increases dopamine receptors are blocked in the hypothalamus-pituitary-axis, as dopamine activity inhibits prolactin release. The pituitary gland is impacted by peripheral active metabolites, hence (in)ability of passing the blood-brain-barrier is considered for the ranking (e.g., risperidone and amisulpride pass poorly and significantly increase prolactin.) This measure allows for objectivity but does not account for the intricacies involved in sexual health and menstruation.

Placebo-response and dosages changed in the last decennia, potentially influencing outcomes of new-versus-old agents. The poor ranking of haloperidol in EPS could be partially attributed to the inclusion of old studies in which extremely high dosages are used. *Leucht et al.*[29] determined that low-dose haloperidol resulted in less EPS than high-dose, nevertheless still more than the other agents. *Huhn et al.* did not analyse the differences over time or dose, though results are fortified by placebo-response adjustment and sensitivity analyses not substantially changing results.

For effectiveness on memory and attention, *van Dijk et al.* used a meta-analysis[40] which compared effectiveness on subdomains of cognition to haloperidol. Unfortunately, clinical studies with a prospective design and large sample size are not published including cariprazine, brexpiprazole or amisulpride. Therefore, ranking remains largely based on this data. Limitations must be emphasized, as open-label studies were included. Although this is not necessarily an exclusion criterion for objective outcomes (i.e., weight gain or prolactin), memory and attention are prone to subjectivity and bias when not properly blinded. Additionally, improvement of cognitive symptoms can be a result of fading psychosis, i.e., a secondary effect of antipsychotics instead of the direct effect of an agent. This complexity adds to the uncertainty of the ranking.

Further limitations need to be discussed. Firstly, there is a higher risk of error due to singular screening of many citations. Due to the time constraint of a research internship, double screening the results of the literature search was unfeasible. All assessments were made by LJ, aided by FD through discussion when doubts arose.

Secondly, the overall level of evidence was poor, although there is variation amongst different categories. Weight gain is the most extensively studied item, followed by hyperprolactinemia, EPS, and effectiveness on psychosis. While memory and attention problems are deemed debilitating for patients, issues of objectivity and profitability might be explanations for the lack of high-level research. Yet, even with the network analyses of *Pillinger et al.* on weight gain and *Huhn et al.*, most results have a low LoE (as measured with the CINeMA rating[15, 16]).

The majority (66%) of RCT's included in *Pillinger et al.* had an unclear risk of bias (16% high, 18% low). Studies not affiliated with pharmaceutical companies are rare, necessitating us to overlook conflict of interest on occasion.

Thirdly, the number of categories and their cut-offs are arbitrary. However, these decisions are open to debate and fortified by the clinical panel.

Lastly, results of the index should not be taken as direct advice and does not replace clinical counselling for multiple reasons. The evidence is based on group statistics and cannot accurately predict how individuals will react to specific agents. Patients in clinical trials are often not representative of the real world, as therapy-resistant patients or patients with first episodes are often excluded from trials, however are (partly) the target audience for the index. There is a risk the evidence cannot be translated to suit these populations. This reinforces the necessity of personal counselling. Moreover, certain factors are not accounted for in the index for which specialised consultation is necessary, e.g. (wish for) pregnancy and lactation. Additionally, hyperprolactinemia, a possible side-effect, increases risk of osteoporosis[47] and breast cancer. Considering women with schizophrenia-spectrum disorders are already at increased risk for breast cancer,[48] additional risk should be avoided when selecting a suitable agent. Furthermore, although risk of seizure is incorporated in the index, cautious use is advised. Lack of effect sizes makes ranking uncertain and thus requires expert consultation for patients with epilepsy or otherwise at risk for seizures. The necessity for counselling is described and emphasized on the results page of the PAC-index. Further considerations are described in Supplement 6.

An important strength of the PAC-index is its comprehensiveness, based on items important to the patients. When properly utilised alongside a clinician, it can improve decision-making, doctor-patient relationship and optimistically, medication adherence. Baryakova[49] finds that interventions only slightly improve adherence statistics. However, those findings may not pertain to this specialised patient population, where the doctor-patient-relationship plays a critical role. An RCT is necessary to evaluate the tools value in therapy and applicability to specific populations.

5. Conclusion

The available evidence on the adverse effects and effectiveness of cariprazine, brexpiprazole and amisulpride is summarised in rankings relative to the 15 most frequently prescribed antipsychotics in the Netherlands. These rankings are used to assign weights in an algorithm for an online tool with which patients can easily apply the best available evidence in their decision-making to choose an antipsychotic medication. The PAC-Index has thus been updated with the newest EMA-approved antipsychotics and has become more refined regarding the other agents. The combination of extensive research data and clinicians experience is translated to an accessible personalised ranking which can empower patients in their choice of antipsychotic medication.

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7. APPENDIX

SUPPLEMENT 1: SEARCH STRATEGY

Domain	Determinant	Outcome	
Patients prescribed antipsychotic medication for non-affective psychosis (schizophrenia spectrum disorders)	1. Cariprazine 2. Brexpiprazole 3. Amisulpride	Side effects (or adverse effects) – Weight gain – Sexual dysfunction (prolactin production on functional level) – Sleep dysfunction (incl. sleepiness, drowsiness, low energy) – Extrapyramidal side effects (or motor effects, incl. dystonia, akathisia, parkinsonism, tremor) – Anticholinergic effects (dry mouth, constipation, urinary difficulty, blurred vision) – Hypersalivation – Nausea – Vertigo (or dizziness) – Creativity (lack of) – Secondary negative symptoms (apathy, anhedonia) – Menstrual disorder	Intended effects (or effectiveness) – Change in psychotic symptoms (or positive symptoms) – Change in depressive symptoms – Cognition (memory and attention)

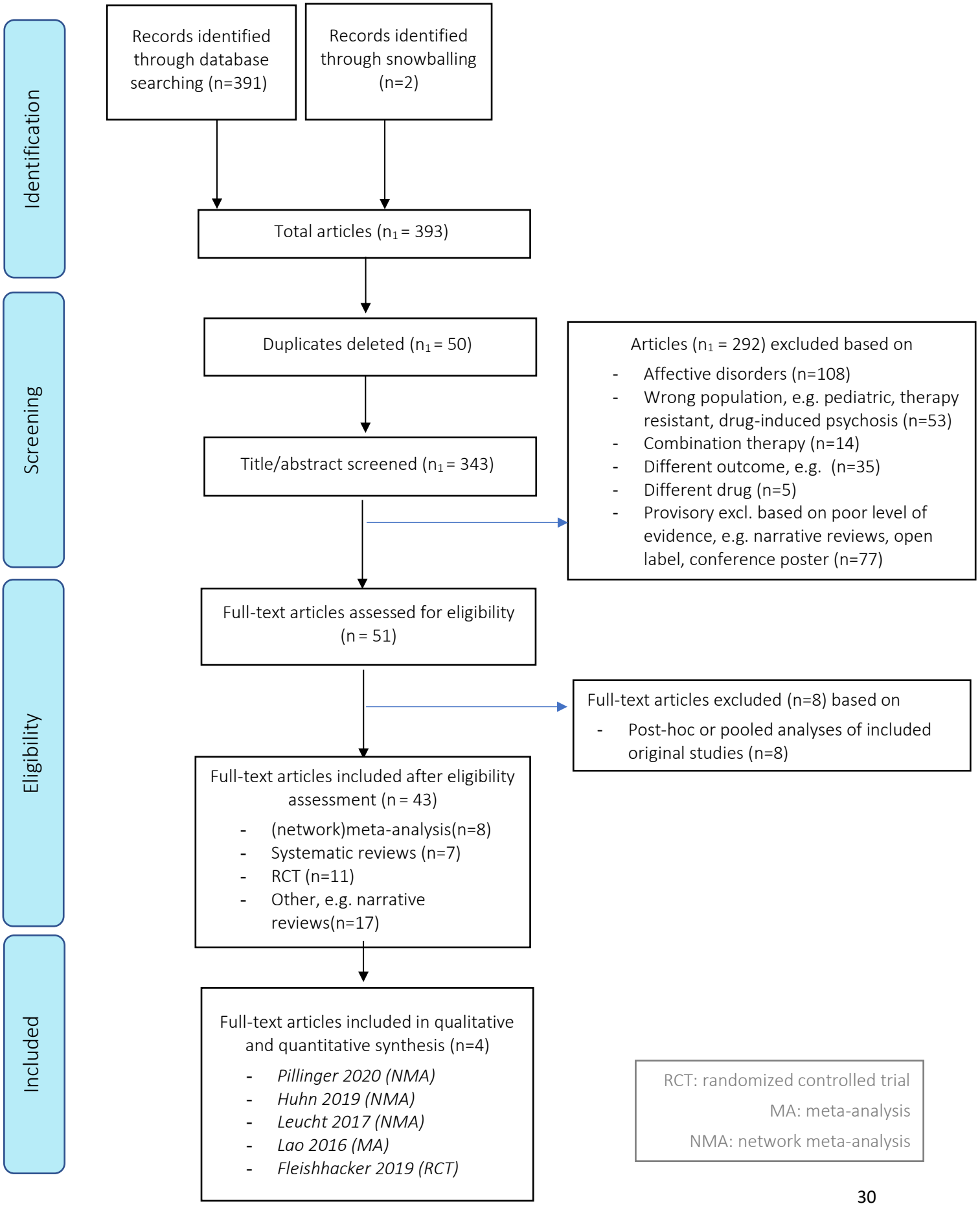
		PubMed	Embase	Cochrane
Cariprazine	Side/adverse [#1]	((("Drug-Related Side Effects and Adverse Reactions"[MeSH Terms] OR "side effect*"[Title/Abstract] OR "adverse effect*"[Title/Abstract]) AND ("Weight Gain"[Title/Abstract] OR "Weight Gain"[MeSH Major Topic] OR "sexual*"[Title/Abstract] OR ("sleep*"[Title/Abstract] OR "slept"[Title/Abstract]) OR "sleep disorder*"[Title/Abstract] OR "sleep disorders, intrinsic"[MeSH Terms] OR "drows*"[Title/Abstract])) OR "extrapyramidal*"[Title/Abstract] OR "motor effect*"[Title/Abstract] OR "secondary negative symptom*"[Title/Abstract] OR "anticholinerg*"[Title/Abstract] OR "hypersalivation"[Title/Abstract] OR ("naus*"[Title/Abstract] OR "Nausea"[MeSH Major Topic]) OR ("Dizziness"[MeSH Terms] OR "dizz*"[Title/Abstract] OR "vertigo"[Title/Abstract]) OR "creativ*"[Title/Abstract] OR "affect*"[Title/Abstract] OR ("Menstruation Disturbances"[MeSH Terms] OR "menstrual dis*"[Title/Abstract] OR "psychotic*"[Title/Abstract] OR "positive symptom*"[Title/Abstract] OR "depressi*"[Title/Abstract] OR "memor*"[Title/Abstract] OR "attention"[Title/Abstract] OR ("Cognition"[MeSH Terms] OR "cognit*"[Title/Abstract]))) AND "cariprazine"[Title/Abstract] **247 results**	('adverse drug reaction'/exp OR (side AND effect*:ti,ab,kw) OR (adverse AND effect*:ti,ab,kw)) AND (('weight gain':ti,ab,kw OR 'body weight gain'/mj) OR sexual*:ti,ab,kw OR (sleep*:ti,ab,kw OR slept*:ti,ab,kw OR 'sleep disorder'/exp OR drows*:ti,ab,kw) OR 'extrapyramidal*':ti,ab,kw OR 'motor effect*':ti,ab,kw OR 'secondary negative symptom*':ti,ab,kw OR 'anticholinerg*':ti,ab,kw OR 'hypersalivation':ti,ab,kw OR (naus*:ti,ab,kw OR 'nausea and vomiting'/exp) OR ('dizziness'/exp OR dizz*:ti,ab,kw OR vertigo:ti,ab,kw) OR creativ*:ti,ab,kw OR affect*:ti,ab,kw OR ('menstruation disorder'/exp OR 'menstrual dis*':ti,ab,kw) OR 'psychotic*':ti,ab,kw OR 'positive symptom*':ti,ab,kw OR depressi*:ti,ab,kw OR memor*:ti,ab,kw OR attention:ti,ab,kw OR ('cognitive defect'/exp OR 'cognitive function test'/exp OR cognit*:ti,ab,kw)) AND cariprazine:ti,ab,kw AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) **132 results**	Cariprazine (title/abstract) **1 result**
	Intended [#2]	**("Treatment Outcome"[Mesh]) AND (("psychotic*"[Title/Abstract]) OR ("positive symptom*"[Title/Abstract]) OR (depressi*[Title/Abstract]) OR (memor*[Title/Abstract]) OR (attention*[Title/Abstract]) OR (("Cognition"[Mesh]) OR (cognit*[Title/Abstract]))) AND (cariprazine[title/abstract]) NOT (search #1)** **0 extra results (43 total)**	'treatment outcome'/exp AND ('psychotic*':ti,ab,kw OR 'positive symptom*':ti,ab,kw OR depressi*:ti,ab,kw OR memor*:ti,ab,kw OR attention:ti,ab,kw OR ('cognitive defect'/exp OR 'cognitive function test'/exp OR cognit*:ti,ab,kw)) AND cariprazine:ti,ab,kw AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) NOT (search #1) **11 extra results**	
	Total hits, for title/abstract screening		**391**	

Brexpiprazole	Adverse [#3]	((("Drug-Related Side Effects and Adverse Reactions"[MeSH Terms] OR "side effect*"[Title/Abstract] OR "adverse effect*"[Title/Abstract]) AND ("Weight Gain"[Title/Abstract] OR "Weight Gain"[MeSH Major Topic] OR "sexual*"[Title/Abstract] OR ("sleep*"[Title/Abstract] OR "slept"[Title/Abstract]) OR "sleep disorder*"[Title/Abstract] OR "sleep disorders, intrinsic"[MeSH Terms] OR "drows*"[Title/Abstract])) OR "extrapyramidal*"[Title/Abstract] OR "motor effect*"[Title/Abstract] OR "secondary negative symptom*"[Title/Abstract] OR "anticholinerg*"[Title/Abstract] OR "hypersalivation"[Title/Abstract] OR ("naus*"[Title/Abstract] OR "Nausea"[MeSH Major Topic]) OR ("Dizziness"[MeSH Terms] OR "dizz*"[Title/Abstract] OR "vertigo"[Title/Abstract]) OR "creativ*"[Title/Abstract] OR "affect*"[Title/Abstract] OR ("Menstruation Disturbances"[MeSH Terms] OR "menstrual dis*"[Title/Abstract] OR "psychotic*"[Title/Abstract] OR "positive symptom*"[Title/Abstract] OR "depressi*"[Title/Abstract] OR "memor*"[Title/Abstract] OR "attention"[Title/Abstract] OR ("Cognition"[MeSH Terms] OR "cognit*"[Title/Abstract]))) AND "brexpiprazole"[Title/Abstract] NOT (search #1) **152 extra results**	(('adverse drug reaction'/exp) OR (side AND effect*:ti,ab,kw) OR (adverse AND effect*:ti,ab,kw)) AND (('weight gain':ti,ab,kw OR 'body weight gain'/mj) OR sexual*:ti,ab,kw OR (sleep*:ti,ab,kw OR slept*:ti,ab,kw OR 'sleep disorder'/exp OR drows*:ti,ab,kw) OR 'extrapyramidal*':ti,ab,kw OR 'motor effect*':ti,ab,kw OR 'secondary negative symptom*':ti,ab,kw OR 'anticholinerg*':ti,ab,kw OR 'hypersalivation':ti,ab,kw OR (naus*:ti,ab,kw OR 'nausea and vomiting'/exp) OR ('dizziness'/exp OR dizz*:ti,ab,kw OR vertigo:ti,ab,kw) OR creativ*:ti,ab,kw OR affect*:ti,ab,kw OR ('menstruation disorder'/exp OR 'menstrual dis*':ti,ab,kw) OR 'psychotic*':ti,ab,kw OR 'positive symptom*':ti,ab,kw OR depressi*:ti,ab,kw OR memor*:ti,ab,kw OR attention:ti,ab,kw OR ('cognitive defect'/exp OR 'cognitive function test'/exp OR cognit*:ti,ab,kw)) AND brexpiprazole:ti,ab,kw AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) NOT (search #1 OR #2) **65 results**	Brexpiprazol (title/abstract) **0 results**
	Intended [#4]	**("Treatment Outcome"[Mesh]) AND (("psychotic*"[Title/Abstract]) OR ("positive symptom*"[Title/Abstract]) OR (depressi*[Title/Abstract]) OR (memor*[Title/Abstract]) OR (attention*[Title/Abstract]) OR (("Cognition"[Mesh]) OR (cognit*[Title/Abstract]))) AND (brexpiprazole[title/abstract]) NOT (search #3)** **1 extra result (full text unavailable)**	'treatment outcome'/exp AND ('psychotic*':ti,ab,kw OR 'positive symptom*':ti,ab,kw OR depressi*:ti,ab,kw OR memor*:ti,ab,kw OR attention:ti,ab,kw OR ('cognitive defect'/exp OR 'cognitive function test'/exp OR cognit*:ti,ab,kw)) AND brexpiprazole:ti,ab,kw AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) NOT (search #3) **6 results**	
	Total for title/abstract screening		**224**	

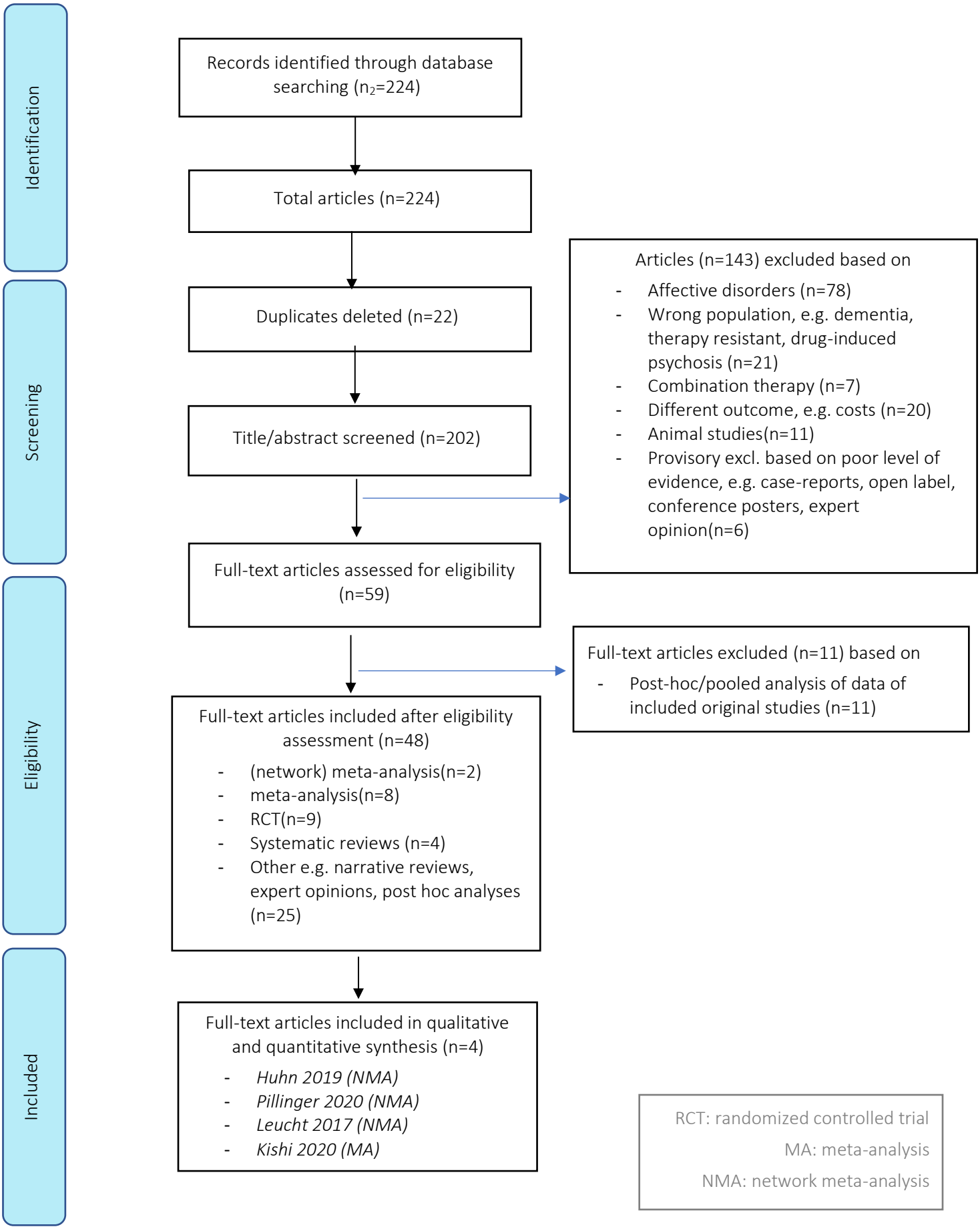
Amilsupride	Adverse [#5]	((("Drug-Related Side Effects and Adverse Reactions"[MeSH Terms] OR "side effect*"[Title/Abstract] OR "adverse effect*"[Title/Abstract]) AND ("Weight Gain"[Title/Abstract] OR "Weight Gain"[MeSH Major Topic] OR "sexual*"[Title/Abstract] OR ("sleep*"[Title/Abstract] OR "slept"[Title/Abstract]) OR "sleep disorder*"[Title/Abstract] OR "sleep disorders, intrinsic"[MeSH Terms] OR "drows*"[Title/Abstract])) OR "extrapyramidal*"[Title/Abstract] OR "motor effect*"[Title/Abstract] OR "secondary negative symptom*"[Title/Abstract] OR "anticholinerg*"[Title/Abstract] OR "hypersalivation"[Title/Abstract] OR ("naus*"[Title/Abstract] OR "Nausea"[MeSH Major Topic]) OR ("Dizziness"[MeSH Terms] OR "dizz*"[Title/Abstract] OR "vertigo"[Title/Abstract]) OR "creativ*"[Title/Abstract] OR "affect*"[Title/Abstract] OR ("Menstruation Disturbances"[MeSH Terms] OR "menstrual dis*"[Title/Abstract] OR "psychotic*"[Title/Abstract] OR "positive symptom*"[Title/Abstract] OR "depressi*"[Title/Abstract] OR "memor*"[Title/Abstract] OR "attention"[Title/Abstract] OR ("Cognition"[MeSH Terms] OR "cognit*"[Title/Abstract])) AND "amisulpride"[Title/Abstract] NOT (search #4) **From 01/09/2014: 251**	('adverse drug reaction'/exp OR (side AND effect*:ti,ab,kw) OR (adverse AND effect*:ti,ab,kw)) AND ('weight gain':ti,ab,kw OR 'body weight gain'/mj OR sexual*:ti,ab,kw OR sleep*:ti,ab,kw OR slept*:ti,ab,kw OR 'sleep disorder'/exp OR drows*:ti,ab,kw OR 'extrapyramidal*':ti,ab,kw OR 'motor effect*':ti,ab,kw OR 'secondary negative symptom*':ti,ab,kw OR 'anticholinerg*':ti,ab,kw OR 'hypersalivation':ti,ab,kw OR naus*:ti,ab,kw OR 'nausea and vomiting'/exp OR 'dizziness'/exp OR dizz*:ti,ab,kw OR vertigo:ti,ab,kw OR creativ*:ti,ab,kw OR affect*:ti,ab,kw OR 'menstruation disorder'/exp OR 'menstrual dis*':ti,ab,kw OR 'psychotic*':ti,ab,kw OR 'positive symptom*':ti,ab,kw OR depressi*:ti,ab,kw OR memor*:ti,ab,kw OR attention:ti,ab,kw OR 'cognitive defect'/exp OR 'cognitive function test'/exp OR cognit*:ti,ab,kw) AND amisulpride:ti,ab,kw AND [01-09-2014]/sd NOT [08-03-2023]/sd AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) NOT (search #4) **143 results**	Amisulpride [title/abstract] from 01/09/2014 **4 results**
	Intended [#6]	(("Treatment Outcome"[Mesh]) AND (("psychotic *"[Title/Abstract]) OR ("positive symptoms"[Title/Abstract]) OR (depressi*[Title/Abstract]) OR (memory[Title/Abstract]) OR (attention[Title/Abstract]) OR (cogniti*[Title/Abstract])) AND ((amisulpride[title/abstract]))) NOT (search #5) **From 01/09/2014: 0**	'treatment outcome'/exp AND ('psychotic*':ti,ab,kw OR 'positive symptom*':ti,ab,kw OR depressi*:ti,ab,kw OR memor*:ti,ab,kw OR attention:ti,ab,kw OR 'cognitive defect'/exp OR 'cognitive function test'/exp OR cognit*:ti,ab,kw) AND amisulpride:ti,ab,kw AND [01-09-2014]/sd NOT [08-03-2023]/sd AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) NOT (search #5) **8 results**	
	Total for title/abstract screening		**406**	

SUPPLEMENT 2: FLOWCHARTS

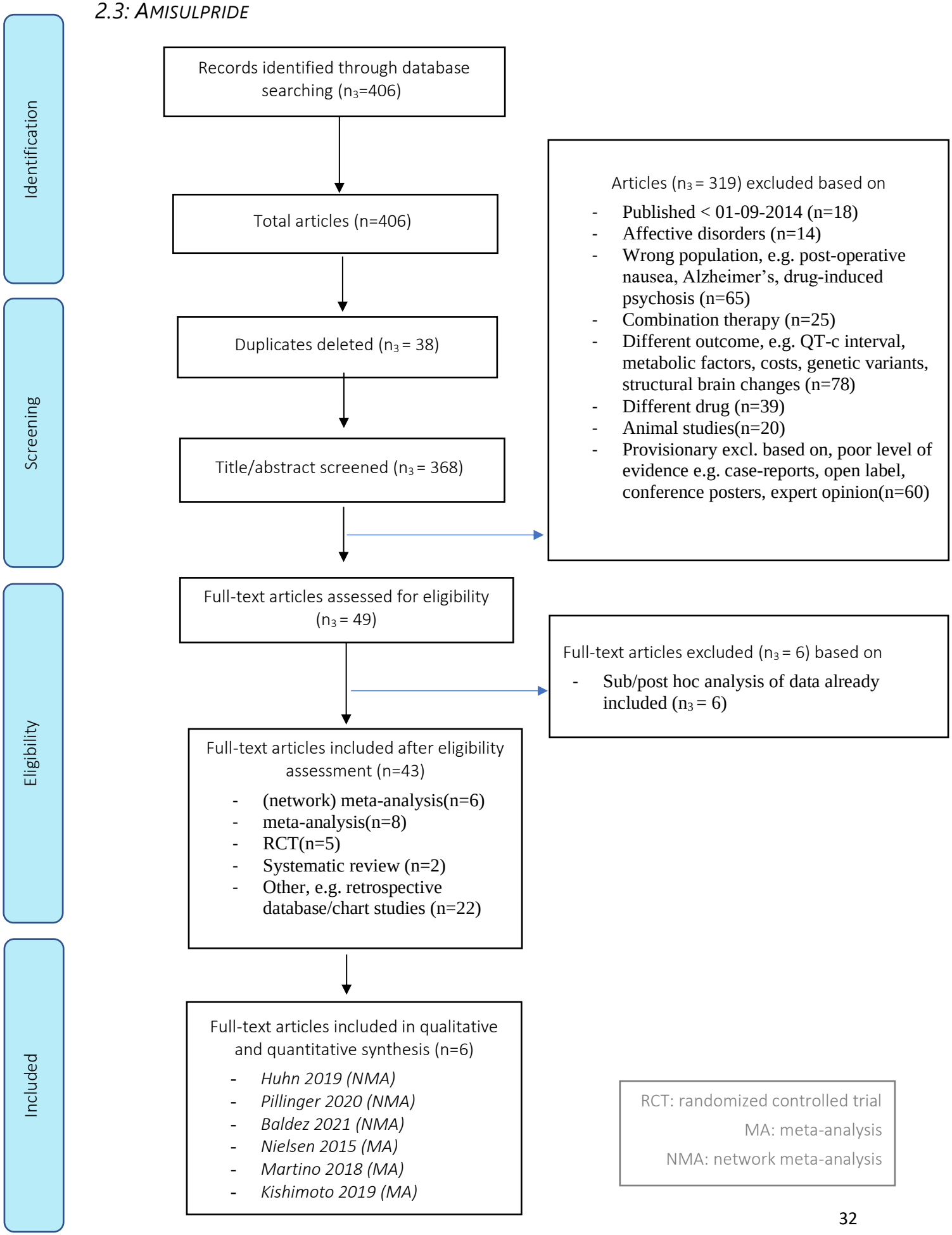
2.1: CARIPRAZINE



2.2: *Brexpiprazole*



2.3: AMISULPRIDE



SUPPLEMENT 3: INCLUDED STUDIES

Table 1: included studies

	Study	Agents	Outcome
Cochrane reviews and Network MA	Pillinger 2020, metabolic function	CAR, BRE, AMI	Weight
	Huhn 2019, comparative analysis*	CAR, BRE, AMI	Effectivity, Weight, social, eps, prolactin, sedation, anticholinergic
	Kishi 2020, (14RCT's , incl ari)	ARI, BRE	PANSS, weight gain, somnolence, akathisia, EPS, dizziness
	Levine 2016 NMA predominant negative symptoms	AMI, PBO	affect
	Millier 2017 NMA efficacy and safety	AMI	Relapse and weight
	Baldez 2021, comparative analysis**	AMI	Cognitive performance
	Zhu 2021 (Huhn + Chinese studies)***	AMI	Prolactin
MA	Lao 2016, tolerability & safety	CAR	EPS, incl akathisia, tremor, restlessness, weight gain, prolactin
	Hagi 2019, metabolic parameters**	CAR, BRE	Weight gain SMD
	Barton 2020, weight gain ****[no access]**	CAR, BRE	
	Generoso 2021, effectivity	CAR	Effectivity, hedges g
	Leucht 2017*	CAR, BRE	
	Demyttenaere 2019	CAR, BRE	Akathisia
	Hagi 2019, metabolic parameters**	CAR, BRE	Weight gain SMD
	Leucht 2017*	CAR, BRE	
	Marder 2017	BRE	PANSS, sedating, weight gain
	Kishi 2018	BRE	Dose related PANSS, CGIS, EPS, weight gain
	Antoun 2020 (14 RCTs, incl. mdd)	BRE	PANSS, CGI_S, PSP, MADRS, akathisia, weight increase, somnolence
	Krause 2018,	AMI	PANSS-neg, SANS, BNSS, depressive and positive symptoms, anti-parkinson medication
	Nielsen 2015	AMI	Cognition
	Martino 2018 overview of Cochrane reviews and MA	AMI	movement disorders (parkinsonism)
	Men 2018 comparative analysis***	AMI, OLA	PANSS, weight gain, constipation, somnolence, insomnia, lactation/amenorrhea/prolactinemia, EPS
	Kishimoto 2019**	AMII	AE, weight gain, prolactin, parkinsonism, sedation and somnolence
	Smith 2019 (using meta-analytic techniques)	AMI, CAR	Effectivity, Prolactin, weight gain…
	Sabe 2021, dose-response meta-analysis	AMI, CAR, BRE	PANSS
	Wu H 2022, dose-response	CAR, BRE, AMI	weight gain
Systematic reviews	Kannarkat 2022, risks of EPS	CAR, BRE	Drug-induced movement disorders (DIMD) and tardive syndromes
	Keks 2020,	CAR, BRE	tolerability
	Barabassy 2021, pooled analysis safety **	CAR	Akathisia (EPS), insomnia, sedation, somnolence, weight gain, cognition impairment, sexual dysfunction
	Corponi 2017	CAR	Effectivity
	Earley 2016, pooled analysis safety and efficacy**	CAR	PANSS, EPS, restlessness, vomiting, weight
	Ivkovic 2017 (beacon, vector, lighthouse, zenith)**	BRE	Prolactin, NCT01397786 and NCT01810783
	Grilli-Tissot 2014 (poster)	AMI	hypersalivation
	Jakobsen 2017 schizotypy/-al		outcomes not described in abstract

RCT	Bose 201, efficacy/safety in acute	CAR	PANSS, EPS scales (AIMS, SAS, BARS)
	Lieberman 2013, efficacy	CAR	PANSS, Parkinsonism (SAS, BARS), Nausea
	Kane 2013, efficacy **	CAR	PANSS, EPS
	Durgam 2014, safety/efficacy acute **	CAR	PANSS, CGI-S, epS
	Durgam 2015, additional analysis**	CAR	PANSS, CGI-S, EPS
	Debelle 2015, neg symptoms	CAR	PANSS-FSPS
	Kane 2015, acute exac.**	CAR	PANSS, CGI-S, EPS, prolactin
	Citrome 2016, hostility*8	CAR	PANSS-hostility
	Nemeth 2016**	CAR	PANSS-FSNS, PSP (personal/social), insomnia
	Szatmari 2019, safety profile**	CAR	EPS, prolactin, weight change, sedation
	Fleishhacker 2019, on neg symptoms**	CAR	Pans (blunted effect)
	Nakamura 2016 (open label)	CAR	EAs and PANSS
	Kane 2014**	BRE	PANSS and CGI-s, insomnia (agitation + headaches), akathisia. NCT01393613**
	Fleischhacker 2015**	BRE	PANSS and CGI-S
	Correl 2015	BRE	PANSS and CGI, akathisia, weight gain, EPS
	Citrome 2016** open label	BRE	PANSS,EPS, weight, Cognition. (NCT02054702,
	Fleischhacker 2017**	BRE	EPS, insomnia, weight gain, PANSS, Depression/anxiety, cognitive test battery
	Ishigooka 2018 (phase I, 2 weeks)**	BRE	Pharmacokinetics, prolactin
	Ishigooka 2018 (phase II/III 6 weeks)**	BRE	Vomiting, nausea, diarrhea, prolactin
	Yoshimura 2019	BRE	Discontinuation due to lack of efficacy, weight gain, eps
	Weiss 2021** (open label)	BRE	PANSS-FSNS, schizophrenia, insomnia, weight increase, akathisia
	Kahn 2018 RCT (OPTiMiSE),	AMI	PANSS, weight
	Hauser 2017 RCT metacognition	AMI	
	Howard 2018 RCT ATLAS (late onset)	AMI	
	Johnsen 2020 rater-blind, RCT (BeSt InTro)	AMI, ARI, OLA	PANSS, weight gain, prolactin,
	Kumar 2014 open label rct	OLA, AMI	for neg sympt and cognitive impairment
Other	**Cariprazine** Expert opinion Werner 2014, expert opinion Citrome 2013, chemical, expert opinion** Fagiolini 2020, recommendations from international panel CAR ** Case studies Fernandes 2021, case series negative symptoms CAR (GCI) Csehi 2022, systematic review of case studies, effectivity, cognitive symptoms CAR (hungary) Kapulsky 2018, case report urinary retention car Poster Barabassy 2018, poster, pooled analysis sexual dysfunction, prolactin and amenorrhoea CAR ** Narrative reviews Fang 2016 (CAR & BRE) negative symptoms and cognitive impairments Frankel 2017 CAR & BRE somnolence Mohr 2021 CAR & BRE efficacies, receptor affinities Morozov 2022 CAR social dysfunction Citrome 2021, narr rev anti-hostility effect of CAR Mohr 2021, narr rev comparing CAR and BRE (NNT efficacy) Torrisi 2020, review cognitive impairments CAR + BRE (receptor affinity) Citrome 2013, clinical efficacy, tolerability** Citrome 2016, review car** Citrome 2018, review CAR**		

Brexpiprazole

Post-hoc analysis

Marder 2021 Post hoc analysis of 6 studies (NCT01396421, NCT01393613, NCT01810380, NCT01668797, NCT01397786, NCT01810783.)

Skuban 2015, pooled results NCT01396421 + NCT01393613 (PANSS, insomnia, akathisia)

Ishigooka 2021 post hoc analysis long term open label study (weight, prolactin, EPS)

Newcomer 2018 pooled analysis weight gain bre

Expert opinion

Citrome 2015 ** expert opinion bre

Hsu 2017, expert opinion bre

Sakurai 2021 japanese expert consensus

Case studies

Kane 2016 overview bre (NCT00905307; NCT01396421; NCT01393613; NCT01649557; NCT01397786) – weight gain, akathisia, sedation

Weiss 2018 analysis short and long term studies bre

Aladeen 2018 case series ari-resistant schizo

Ichinose 2021 case series switching to BRE (EPS, prolactin, weight, PANSS)

Other

Obara 2019 trial on anticholinergic activity bre

Maman 2019, bre vs lurasidone (meta-analysis)

Inoue 2021 retrospective continuation rate

Amisulpride

Retrospective study

Pridan 2014 retrosp chart review older patients, mortality rate

Ryu 2015 retrosp study tardive dyskinesie and -dystonia

Guo 2022, Chinese descriptive analyseis, amisulpride-pollakiuria,

Jha 2022, indian comparative study of efficacy and safety AMI x ARI, PANSS, weight gain, EPS

Berrahal 2016 retrosp study parkinsonism, hypersalivation, weight gain, erectile dysfunction and decreased libido

Garcia 2016 retrosp descriptive study sexual dysfunction (UKU) and amenorrhea

Fernandez 2017 descript retrospect study hyperprolactinemia

Lin CH 2021, retrosp study laxative use with AP

Prospective study

Ramesh 2016 prosp comparative study 6m amisulpride vs olanzapine, overall effectivity, cognitive assessment

Lucca 2017 prosp observational study 5y, weight gain, menstrual irregularity, tardive dyskinesia ami

Drosos 2022 prosp cohort AP trajectory of effectiveness

Database AE

Druschky 2020 observational pharmacovigilance programme, parkinsonism AP AMI

Oh S 2022 AE reporting system database korean AMI sedation, nausea, constipation, dizziness

Other studies

Graf 2014 fMRI study with sexual stimulus (no change with ami)

Oh GH 2015 mixed treatment comparison ami/cloz/ola/ari/quet/zipra

During 2019 expl study, sexual side effects linked hyperprolactemia after 6w ami (D2/3 receptor block)

Nielsen 2022, cohort, comparative ARI x AMI neg and cognitive symptoms

Farheen 2022, cross sectional study medication adherence, PANSS, concentration, memory, depression, constipation, ewight gain, orgasmic dysfunction

Narr review

Vinkers 2015 narr review ami

Murru 2015 narr review hyperprolactinemia

Solmi 2017 narr review ami bre car, safety and tolerabitliy

Gorska 2019 narr review antipsychotic drugs in epilepsy

*handpicked/snowball

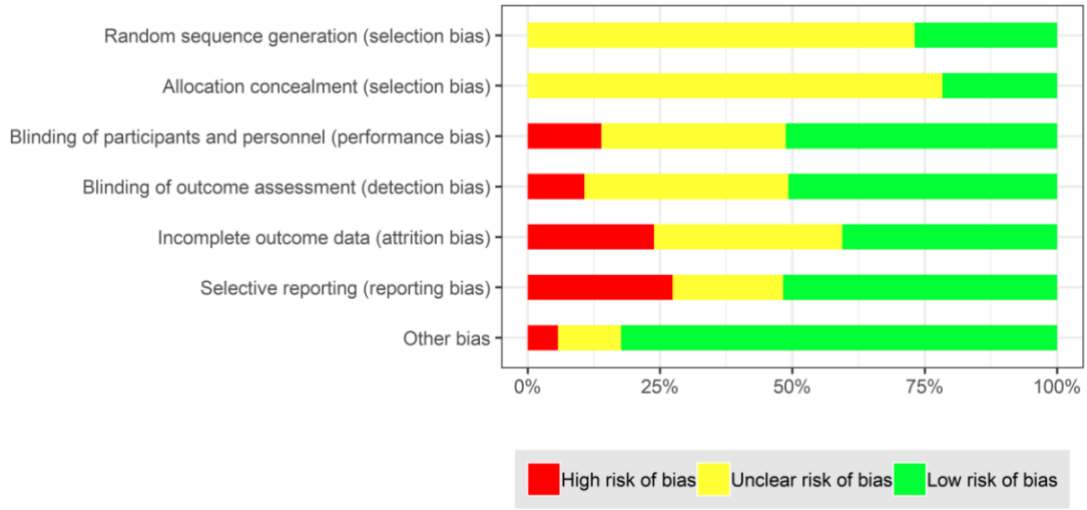
**Conflict of Interest: affiliated or funded by pharma

CAR: Cariprazine, BRE: brexpiprazole, AMI: amisulpride

SUPPLEMENT 4: RISK OF BIAS ASSESSMENTS

Huhn 2019

Huhn supplied a summary of the individual risk assessments.



Subsequently they used the CINeMA rating to estimate confidence in the outcome. Below the agents and outcomes relevant to this research have been summarized.

	CAR	BRE	AMI
WEIGHT	Low	Moderate	Moderate
PROLACTIN	Very low	Low	Low
SEDATION	very low	low	Moderate
PARKINSON MEDICATION	Very low	Low	Low
ANTICHOLINERGIC EFFECTS	Very low	Low	Low
EFFECTIVENESS OVERALL	Low	Low	Moderate
EFFECTIVENESS DEPRESSIVE SYMPTOMS	Moderate	Low	High

green=high, blue=moderate, grey=low, red=very low.

Pillinger 2020

Of the 100 studies included, 18 studies had an overall low risk of bias (18%). 16 studies had a high risk of bias (16%). Post hoc analyses were done to asses effect without these studies, which showed broadly similar treatment effects, and minimal change in heterogeneity and inconsistency assesments. The majority, 66% had an unclear risk of bias, mostly in the allocation concealment and selective reporting domains. Confidence in results for weight gain were low for cariprazine and very low for brexpiprazole and amisulpride.

- Correl 2016: unclear allocation + high risk of selective reporting
- All durgam: unclear allocation, rest low risk
- Early ditto
- Ishigooka 2018: low risk
- Kane 7, 8, 10, 11: much unclear
- Kane ’14: low risk
- Marder ’07: low risk

SUPPLEMENT 5: SUMMARY OF RANKING CAR/BRE/AMI

Table 1: Summary of Ranking + comparison with original			
	Cariprazine	Brexpiprazol	Amisulpride (old ranking)
Weight gain	1/3	1/3	1/3 (1/3)
Prolactin (sexual and menstrual dysfunction)	1/4	2/4	4/4 (3/4)
Sedation and sleep problems	1/4	2/4	2/4 (1/4)
Extrapyramidal symptoms	3/4	2/4	2/4 (4/6)
Anticholinergic effects	1/3	0/3	1/3 (1/4)
Hypersalivation	1/4	1/4	2/4 (2/5)
Nausea	2/3	1/3	2/3 (*/2)
Dizziness	1/3	2/3	0/3 (1/3)
Tired quicker	2/2	2/2	2/2 (2/2)
Blunted affect	1/2	1/2	1/2 (2/2)
Effectiveness on psychotic symptoms	1/4	1/4	4/4 (2/3)
Effectiveness on depressive symptoms	3/4	1/4	3/4 (3/4)
Effectiveness on memory and concentration problems	1/1	*/4	*/4 (*/4)
Route of administration	Tablets daily		
Risk of insult	*/4		
*: insufficient/ambiguous data			

SUPPLEMENT 6: QUESTIONNAIRE

Considerations concerning the rankings are presented alongside the corresponding tables, and expanded on in the discussion section of the paper regarding sexual dysfunction, EPS and memory and attention problems.

1.Weight gain
Q: how acceptable is it if you would gain weight due to your antipsychotic medication?

2.Sexual dysfunction

Q: how acceptable is it if you would experience less desire to make love or have problems to have an orgasm due to your antipsychotic medication? How acceptable would it be for you if your erection becomes less strong?

3.Drowsiness/Sedation

Q: How acceptable is it if you get drowsy or slow due to your antipsychotic medication?

4.Sleep
Q: how acceptable is it if you sleep more or have more difficulty waking up due to your antipsychotic medication?

Considerations concerning the ranking are presented alongside the table for sedation.

5.Extrapyramidal side effects
Q: how acceptable is it if you would experience muscle stiffness, tremors or restless movements due to your antipsychotic medication?
Note: EPS is a dose-related effect of antipsychotics

6./7./8./9. Anticholinergic effects

Q: How acceptable is it if, due to your antipsychotic medication, you will…

…have blurred vision?

…be urinating less smoothly?

…get constipated more often?

…have dry mouth more often?

10.Hypersalivation

Q: How acceptable would it be if you produced more saliva due to your antipsychotic medication?

11.Nausea

Q: How acceptable is it if you would experience nausea more often due to your antipsychotic medication?

12.Dizziness

Q: How acceptable is it if you would experience dizziness more often due to your antipsychotic medication?

Note: dizziness is often a dose-related effect of antipsychotics.

13.Get tired more quickly

Q: How acceptable is it if you would get tired more quickly due to your antipsychotic medication?

14.Blunted affect + need for companionship

Q: How acceptable is it if you become flatter, less creative and less interested in companionship due to your antipsychotic medication?

15.Menstrual disorder

Q: How acceptable is it if your period occurred less often due to your antipsychotic medication?

Considerations concerning the ranking are presented alongside the table for sexual dysfunction.

16.Effectiveness – Overall change in symptoms

Q.: Antipsychotics differ slightly in how well they work. Some agents are more effective than others. How important is it for you that an antipsychotic reduces your psychotic symptoms as much as possible?

17.Effectiveness - Depressive symptoms

Q: How important is it for you that an antipsychotic improves your depressive symptoms as much as possible?

18.Effectiveness - Memory and attention problems

Q: How important is it for you that an antipsychotic improves your memory and concentration problems? Or how important is it that an antipsychotic does not further impair your memory and concentrations problems?

19.Routes of administration

Q: What kind of administration do you prefer?

1. *Tablets daily*
2. *1-2 tablets per week*
3. *Fluid administration daily (droplets and/or grinded and dissolved tablets)*
4. *Depot injection (ranging from every fortnight to every 6 weeks)*

20. Additional questions concerning patient characteristics

QA: Do you smoke?

1. *Yes*
2. *No*

QB: Have you ever suffered an epileptic seizure?

1. *Yes*
2. *No*

QC: Are you pregnant or do you want to become pregnant and breastfeed?

1. *Yes*
2. *No*

A: Smoking

Considerations

This item is not ranked or included in the algorithm. Smoking cigarettes can warrant a dose increase of clozapine. A remark of this is included in the PAC-Index.

B: Epileptic seizure

Considerations concerning the ranking are presented with the table.

B: Pregnancy wish and lactation

Considerations

This item is not ranked or included in the algorithm as advice requires individual risk assessments, of which patients will be notified in the case of a pregnancy wish. Information links will be provided in the PAC-Index.

The RIVM (Dutch National Institute for Public Health and the Environment) and GGZ Trimbos Instituut (Dutch national mental health institute) guidelines are based on a systematic review by Gentile from 2010, leading to 4 recommendations.

1. Antipsychotic medication is necessary during pregnancy when the patient is psychotic. Fetal malformations have occurred with antipsychotic use, but it is unknown if it is caused by the agent or the psychotic disorder.
2. If psychosis occurs during pregnancy in someone who is antipsychotic naïve, it is recommended to prescribe a first-generation antipsychotic (FGA). Weight gain, associated with olanzapine, quetiapine, and risperidone, increases risk of fetal malformations.
3. When pregnancy occurs in someone using antipsychotics, it is advised to continue, as switching is associated with a higher risk than the risk of teratogenic (or other) effects.
4. Discontinuing the antipsychotic agent towards the end of pregnancy diminishes the risk of EPS and insults in the neonate. Weigh this against the risk of recurrent psychosis and consider stopping.

There have been no updates.