Atypical Antipsychotics as Adjuvant Therapy for the Treatment of MDD: Clinical Evidence

Systematic Review

Washington P&T Committee Meeting

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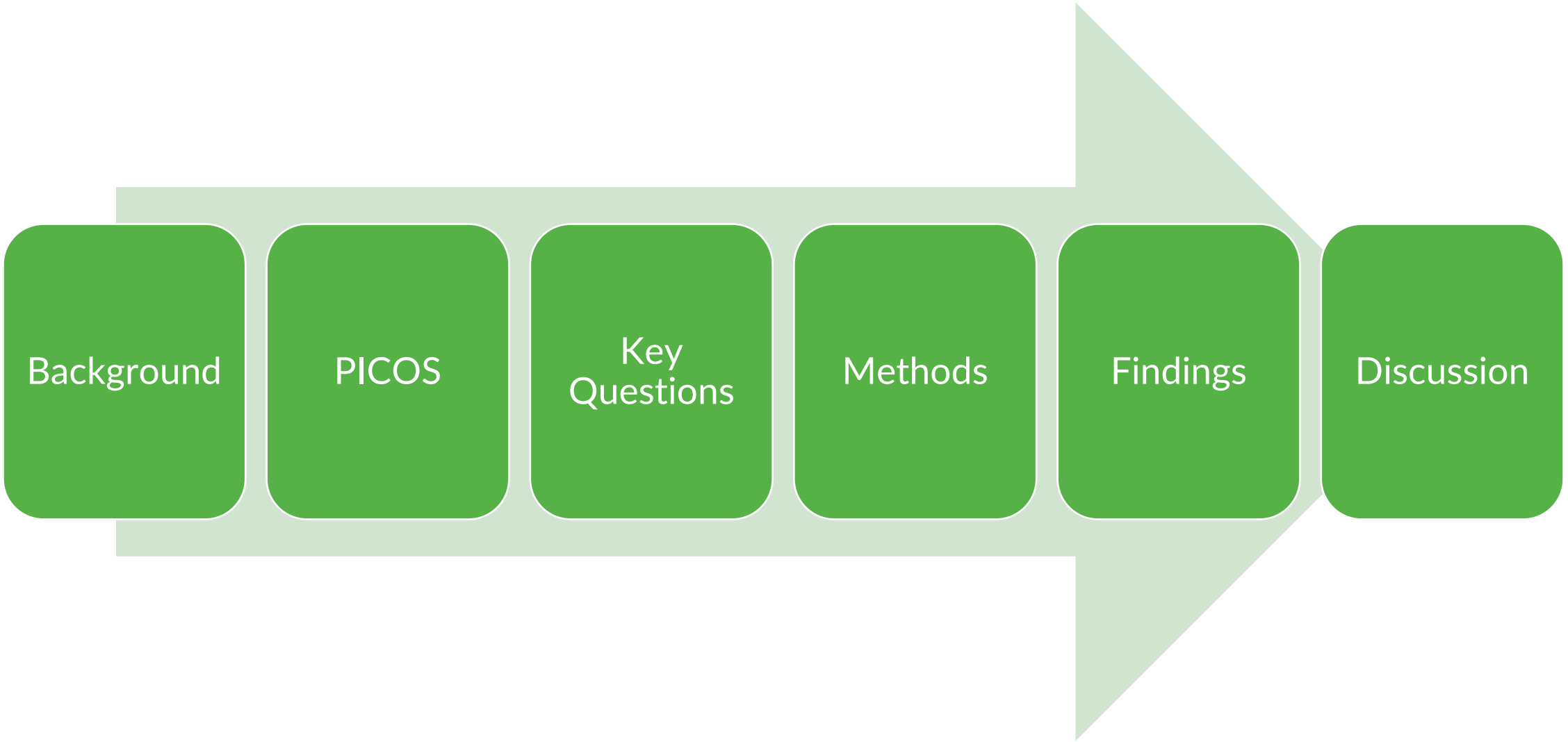
Presented by Wesley Lindsey, PharmD

OHSU

Overview


Background
PICOS
Key Questions
Methods
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Discussion

Background

- Major depressive disorder (MDD) has a lifetime prevalence of 21% in the US, and is ranked as the leading cause of disability worldwide
- 50% of those with depression will experience recurrent episodes
- Guideline-based strategies to achieve remission include addition of lithium or atypical “second-generation” antipsychotics (SGAs) to antidepressant therapy in cases of treatment-resistant depression (TRD)
- SGAs appear to be preferred by patients as a strategy for antidepressant augmentation over first-generation antipsychotics

PICOS

- Populations:
  - Adults with MDD
- Interventions:
  - FDA-approved interventions
    - Aripiprazole
    - Brexpiprazole
    - Cariprazine
    - Olanzapine + fluoxetine
    - Quetiapine

PICOS

- Interventions (continued):
  - Atypical antipsychotics used off-label for adjunctive treatment of MDD
    - Asenapine
    - Clozapine
    - Iloperidone
    - Lumateperone
    - Lurasidone
    - Paliperidone
    - Pimavanserin (pipeline agent)
    - Risperidone
    - Ziprasidone
- Comparators:
  - Another listed intervention
  - Standard of care
  - Placebo

PICOS

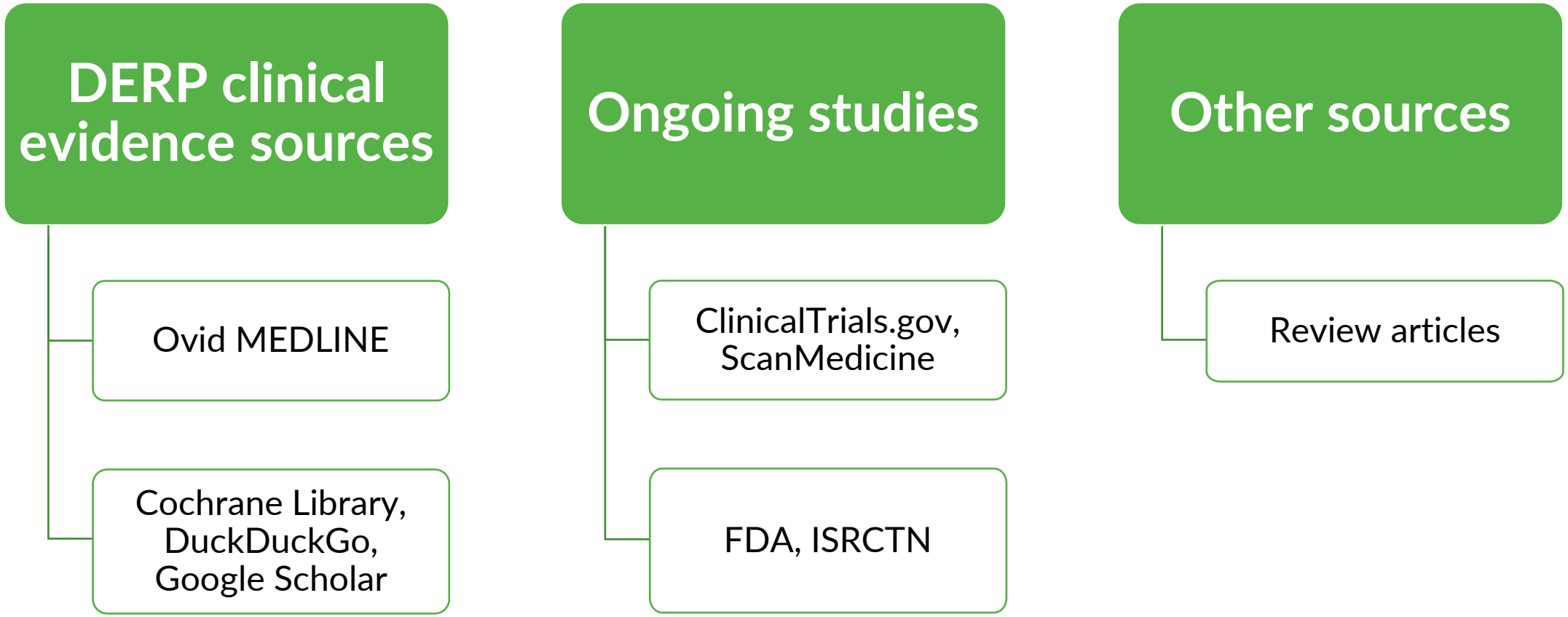
- Outcomes:
  - Depression severity
  - Quality of life (QoL)
  - Function
  - Suicidal behavior/risk
  - Adverse events (AEs)
  - Serious adverse events (SAEs)
- Study Designs:
  - Randomized control trials (RCTs)

Key Questions

1. Effectiveness
    a. Variation by patient characteristic (e.g., age, duration of MDD)
2. Harms
    a. Variation by patient characteristic (e.g., age, duration of MDD)
3. Characteristics of ongoing studies and selected pipeline agents
    a. Pimavanserin
    b. Lumateperone tosylate

Methods

Methods



Abbreviations. DERP: Drug Effectiveness Review Project; FDA: US Food and Drug Administration; ISRCTN: International Standard Randomized Controlled Trial Number (registry).

Methods

- Searched DERP clinical evidence sources from inception to October 20, 2023
- Examined reference lists of systematic reviews
- Assessed the risk of bias (RoB) of included studies
- Used GRADE approach for overall certainty of evidence for critical outcomes
- Searched ClinicalTrials.gov, ISRCTN, ScanMedicine, and FDA resources for ongoing studies

Abbreviations. DERP: Drug Effectiveness Review Project; FDA: US Food and Drug Administration; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; ISRCTN: International Standard Randomized Controlled Trial Number.

DERP Risk of Bias Assessment

- **Low**

  Clear reporting of methods and mitigation of potential biases and conflicts of interest

- **Moderate**

  Incomplete information about methods that might mask important limitations or a meaningful conflict of interest

- **High**

  Clear flaws that might introduce serious bias

GRADE Certainty of Evidence

Outcomes Rated: *MADRS, HAM-D17, CGI-I, response, BARS, change in body weight*

- **High** *(RCTs start here)*
  Very confident that the estimate of effect of intervention on outcome lies close to the true effect
- **Moderate**
  Moderately confident in estimate of effect of intervention on outcome; true effect is likely close to estimate, but possibly different
- **Low**
  Little confidence in estimate of effect of intervention on outcome; true effect may be substantially different from estimate
- **Very Low**
  No confidence in estimate of effect of intervention on outcome; true effect is likely substantially different from estimate

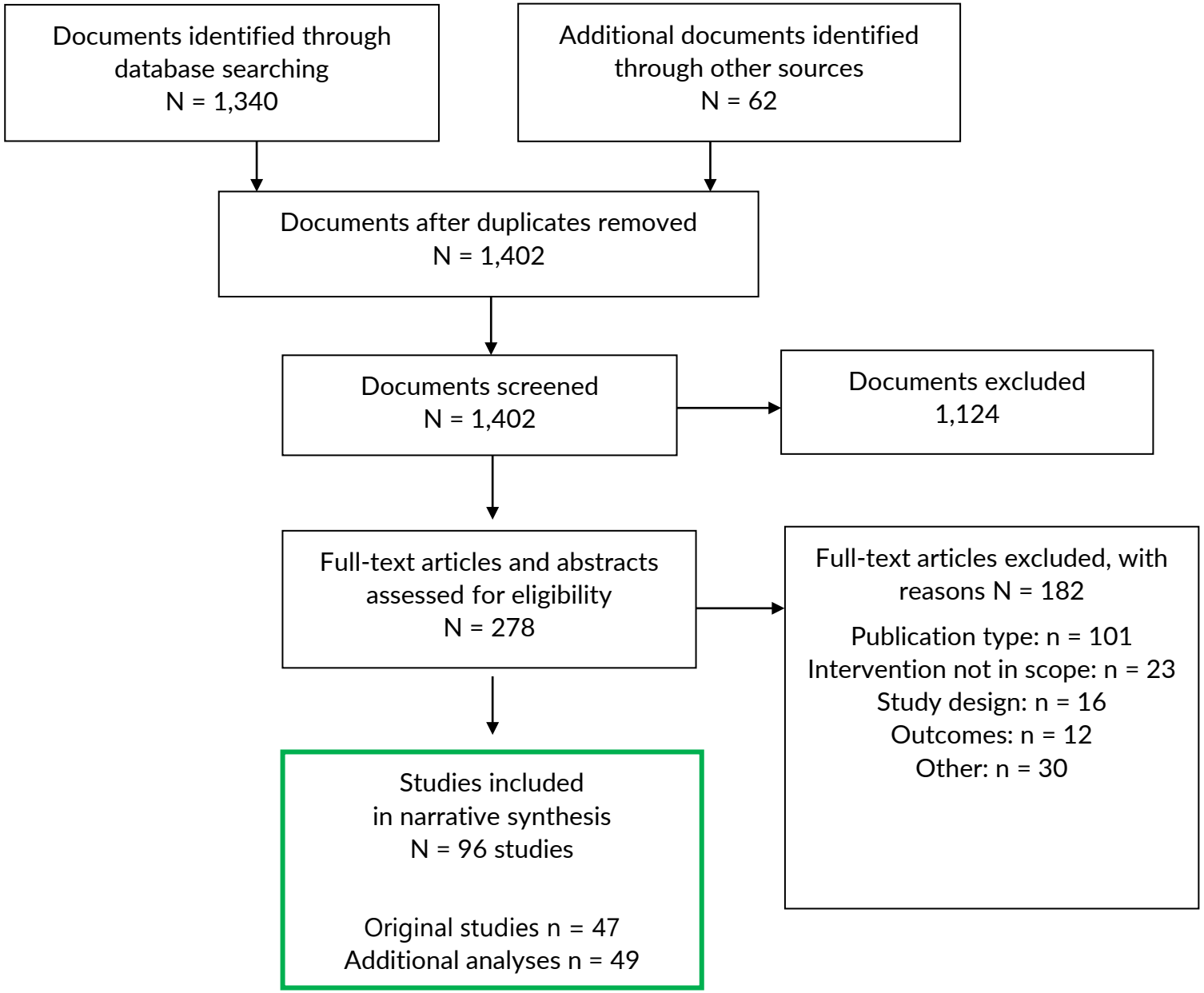
Abbreviations. CGI-I: Clinical Global Impressions-Improvement; BARS: Barnes Akathisia Rating Scale; HAM-D17: 17-item Hamilton Depression Rating Scale; MADRS: Montgomery-Asberg Depression Rating Scale.

Meta-Analysis

- Evaluable results were assessed with Review Manager (RevMan) 5.4
  - Not all studies reported results that could be analyzed
- Focused on GRADE outcomes
- See report Appendix C for meta-analysis figures

Findings

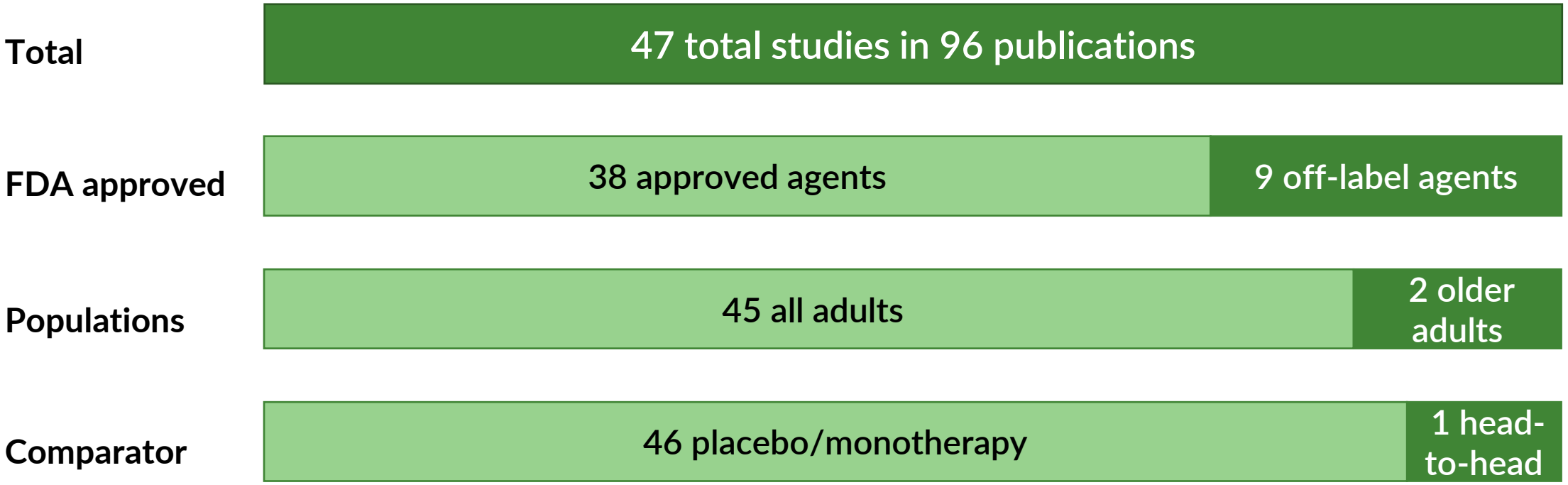
Study Flow Diagram



Common Clinical Outcomes Measured

- Depression
  - Montgomery-Asberg Depression Rating Scale (MADRS)
  - Hamilton Depression Rating Scale (17-item; HAM-D17)
- Overall improvement
  - Clinical Global Impressions (CGI) scale
  - Response
  - Remission
- AEs
  - Barnes Akathisia Rating Scale (BARS)
  - Abnormal Involuntary Movement Scale (AIMS)

Findings: Study Characteristics



All participants received some type of antidepressant treatment (ADT)

Findings: Study Characteristics: FDA-Approved Adjunctive SGAs

Therapy	Number of RCTs	Study Size Range	N	Study Duration, (weeks)
Aripiprazole	12	52 to 1,522	4,846	6 to 12
Brexpiprazole	5	379 to 886	2,839	6 to 26
Cariprazine	5	231 to 819	3,083	6 to 8
Olanzapine/fluoxetine	5	28 to 605	2,060	8 to 27
Quetiapine XR	10	36 to 688	2,123	6 to 12
Total	**37 studies (in 78 publications)**		**14,951**	**6 to 27**

Findings: Study Characteristics: FDA-Approved Adjunctive SGAs

Comparators	Number of RCTs	Study Size Range	N	Study Duration, (weeks)
Aripiprazole vs. Olanzapine vs. Lithium	1	30	30	4 weeks
Total	**1 study** (in 1 publication)			

Findings: Study Characteristics: Non-FDA Approved Adjunctive SGAs

Therapy	Number of RCTs	Study Size Range	N	Study Duration, (weeks)
Pimavanserin	2	203 to 298	501	6 to 10
Risperidone	5	24 to 489	968	4 to 24
Ziprasidone	2	64 to 139	203	8
Total	**9 studies** (in 17 publications)		**1,672**	**4 to 24**

There were no published studies for the use of asenapine, clozapine, iloperidone, lumateperone, lurasidone, or paliperidone as adjunctive treatment for MDD

Aripiprazole

Aripiprazole: Overview

- Study characteristics:
  - 12 RCTs
  - 23 additional publications
    - 8 secondary/post hoc analyses
    - 15 pooled analyses
  - 2 RCTs in older adults
  - Most studies had a run-in period to confirm TRD

Findings: Aripiprazole vs. Placebo or ADT Monotherapy: Efficacy

MADRS

- 9 RCTs, N = 2,795
- **GRADE: High**
  - MADRS scores typically improved 2 to 3 points during initial treatment

CGI-I

- 8 RCTs, N = 3,874
- **GRADE: High**
  - Modest improvement in CGI-Improvement (CGI-I) scores

Response

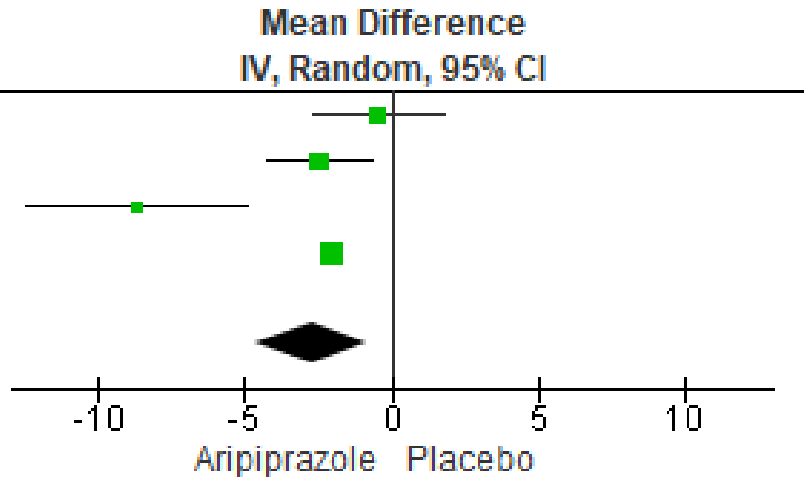
- 9 RCTs, N = 3,975
- **GRADE: Moderate**
  - Aripiprazole showed higher rates of response (10% to 28% absolute change)

Findings: Aripiprazole: Change in MADRS

	Aripiprazole			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Fava 2012	-8.54	7.21	54	-8.09	8.13	167	23.2%	-0.45 [-2.73, 1.83]
Fava 2012	-5.8	7.08	61	-3.32	1.51	93	26.7%	-2.48 [-4.28, -0.68]
Han 2015	-16.3	9.19	50	-7.6	9.7	46	14.4%	-8.70 [-12.49, -4.91]
Kamijima 2018	-9.2	0.5	208	-7.2	0.5	203	35.6%	-2.00 [-2.10, -1.90]
Total (95% CI)			**373**			**509**	**100.0%**	**-2.74 [-4.60, -0.87]**

Heterogeneity: Tau² = 2.54; Chi² = 14.06, df = 3 (P = 0.003); I² = 79%

Test for overall effect: Z = 2.87 (P = 0.004)

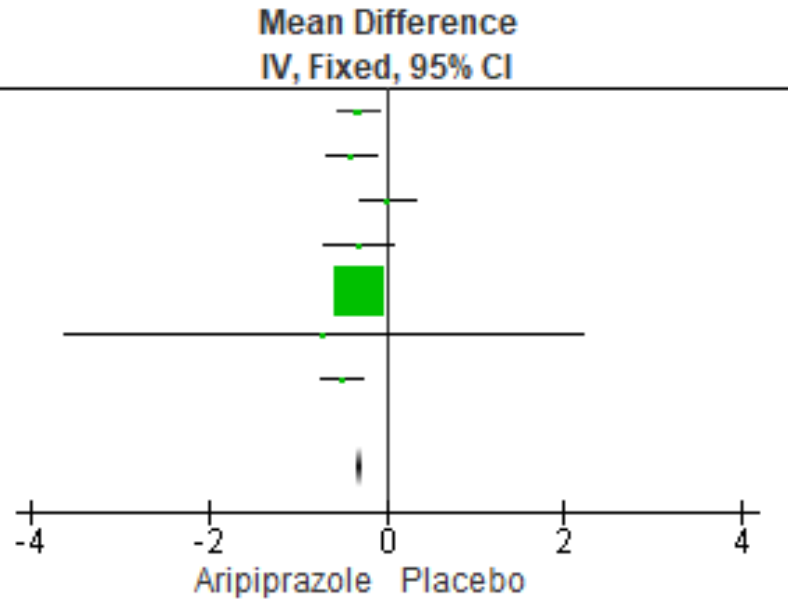


Findings: Aripiprazole: CGI-Improvement

	Aripiprazole			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Berman 2007	2.49	1.0763	181	2.81	1.1803	172	0.7%	-0.32 [-0.56, -0.08]
Berman 2009	2.4	1.3304	177	2.8	1.3115	172	0.5%	-0.40 [-0.68, -0.12]
Fava 2012	3.69	0.96	52	3.68	1.11	162	0.4%	0.01 [-0.30, 0.32]
Fava 2012	3.41	1.14	58	3.72	0.97	61	0.3%	-0.31 [-0.69, 0.07]
Kamijima 2018	2.6	0.1	208	2.9	0.1	203	97.5%	-0.30 [-0.32, -0.28]
Lin 2011	1.29	2.2455	21	2	6.3057	20	0.0%	-0.71 [-3.64, 2.22]
Marcus 2008	2.4	1.0881	185	2.9	1.0852	184	0.7%	-0.50 [-0.72, -0.28]
Total (95% CI)			**882**			**974**	**100.0%**	**-0.30 [-0.32, -0.28]**

Heterogeneity: $Chi^2 = 7.51$, $df = 6$ ($P = 0.28$); $I^2 = 20\%$

Test for overall effect: $Z = 30.89$ ($P < 0.00001$)

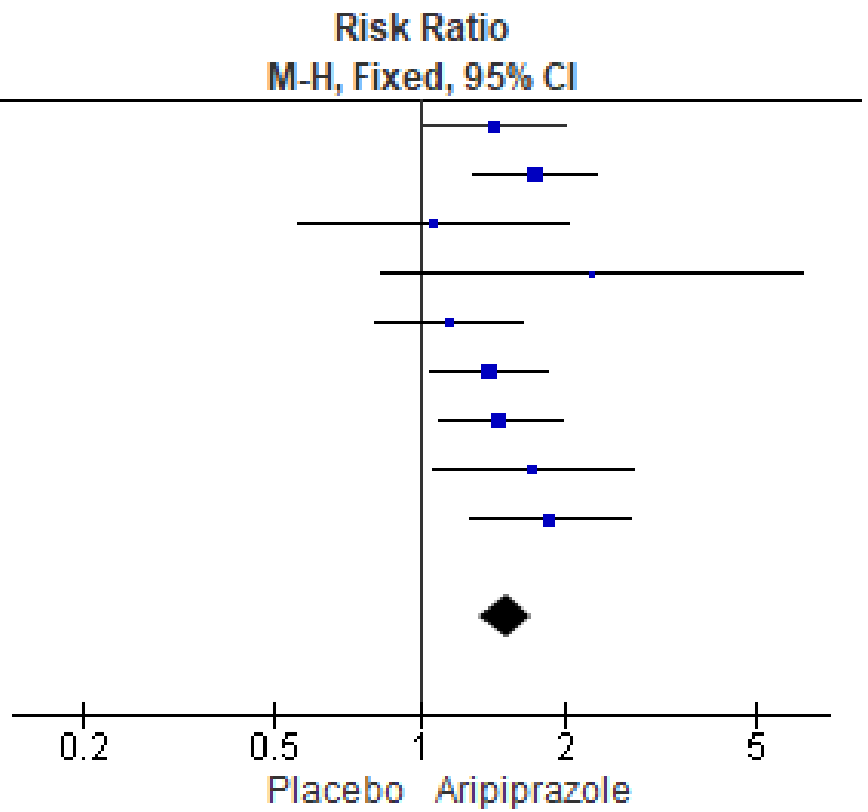


Findings: Aripiprazole: MADRS Response

Study or Subgroup	Aripiprazole Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Berman 2007	61	181	42	178	15.0%	1.43 [1.02, 1.99]
Berman 2009	82	177	46	172	16.5%	1.73 [1.29, 2.32]
Fava 2012	10	54	29	167	5.0%	1.07 [0.56, 2.04]
Fava 2012	11	61	5	63	1.7%	2.27 [0.84, 6.16]
Han 2015	30	50	24	46	8.8%	1.15 [0.80, 1.64]
Kamijima 2013	76	194	55	195	19.4%	1.39 [1.05, 1.85]
Kamijima 2018	78	208	52	203	18.6%	1.46 [1.09, 1.96]
Lin 2011	18	21	10	20	3.6%	1.71 [1.07, 2.75]
Marcus 2008	60	185	32	184	11.3%	1.86 [1.28, 2.72]
Total (95% CI)		**1131**		**1228**	**100.0%**	**1.51 [1.33, 1.71]**
Total events	426		295			

Heterogeneity: $Chi^2 = 6.77$, $df = 8$ ($P = 0.56$); $I^2 = 0\%$

Test for overall effect: $Z = 6.52$ ($P < 0.00001$)



Findings: Aripiprazole: Harms

BARS

- 7 RCTs, N = 2,372
- **GRADE: Moderate**
  - Aripiprazole showed modestly higher scores (increase in akathisia)

Change in body weight

- 11 RCTs, N = 4,208
- **GRADE: High**
  - Aripiprazole typically showed 1 kg to 1.5 kg increase in body weight in the first 6 weeks of therapy

Findings: Aripiprazole: Subpopulations

- Factors noted in specialty populations:
  - Improved rates of response/remission for individuals with:
    - Employment
    - Less severe symptoms at enrollment
  - Did not impact response/remission
    - Age
    - Baseline hostility/anger

Brexpiprazole

Brexpiprazole: Overview

- Study characteristics:
  - 5 RCTs
  - 12 additional publications
    - 12 pooled analyses
  - Most studies had a run-in period to confirm TRD

Findings: Brexpiprazole vs. Placebo: Efficacy

MADRS

- 5 RCTs, N = 2,829
- **GRADE: High**
  - MADRS scores typically improved 1.5 to 3 points during treatment

CGI-I

- 4 RCTs, N = 2,326
- **GRADE: Moderate**
  - Modest improvement in CGI-I scores, with inconsistent results

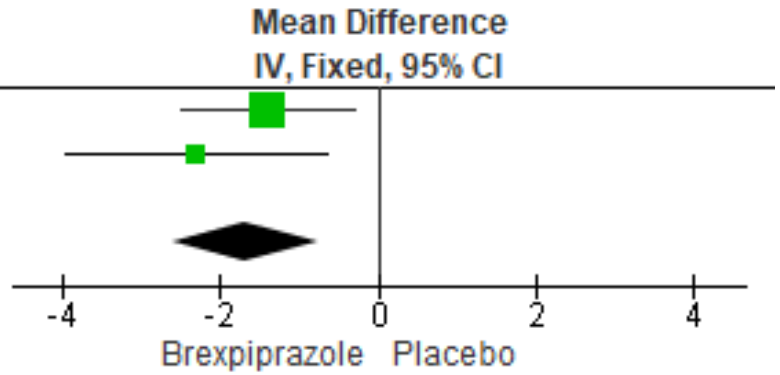
Response

- 5 RCTs, N = 2,829
- **GRADE: Moderate**
  - Brexpiprazole showed higher rates of response (4% to 12% absolute change)

Findings: Brexpiprazole vs. Placebo: Change in MADRS

Study or Subgroup	Brexpiprazole Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Hobart 2018 (CMRO)	-6	5.5281	191	-4.6	5.7271	205	69.2%	-1.40 [-2.51, -0.29]
Hobart 2018 (Psychi)	-10.4	8.2922	191	-8.1	8.5276	202	30.8%	-2.30 [-3.96, -0.64]
Total (95% CI)			**382**			**407**	**100.0%**	**-1.68 [-2.60, -0.75]**

Heterogeneity: Chi² = 0.78, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 3.56 (P = 0.0004)

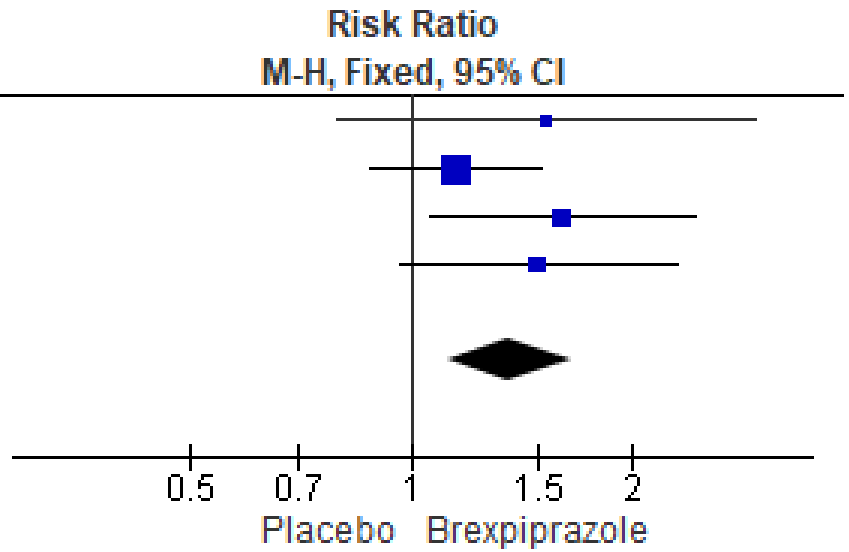


Findings: Brexpiprazole vs. Placebo: Response

Study or Subgroup	Brexpiprazole Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hobart 2018 (CMRO)	20	191	14	205	10.0%	1.53 [0.80, 2.95]
Hobart 2018 (Psychi)	72	191	66	202	47.5%	1.15 [0.88, 1.51]
Thase 2015 Polaris	49	213	29	203	22.0%	1.61 [1.06, 2.44]
Thase 2015 Pyxis	41	175	28	178	20.5%	1.49 [0.97, 2.30]
Total (95% CI)		**770**		**788**	**100.0%**	**1.36 [1.12, 1.65]**
Total events	182		137			

Heterogeneity: Chi² = 2.37, df = 3 (P = 0.50); I² = 0%

Test for overall effect: Z = 3.13 (P = 0.002)



Findings: Brexpiprazole vs. Placebo: Harms

BARS

- 3 RCTs, N = 1,932
- **GRADE: High**
  - Brexpiprazole showed modestly higher scores (increase in akathisia)

Change in body weight

- 5 RCTs, N = 2,829
- **GRADE: High**
  - Brexpiprazole typically showed 1 kg to 1.6 kg increase in body weight in the first 6 weeks of therapy

Cariprazine

Findings: Cariprazine vs. Placebo: Efficacy

MADRS

- 5 RCTs, N = 3,068
- **GRADE: High**
  - MADRS scores typically improved 1 to 3 points during initial treatment

CGI-I

- 5 RCTs, N = 3,068
- **GRADE: Moderate**
  - Modest improvement in CGI-I scores that were typically not significant

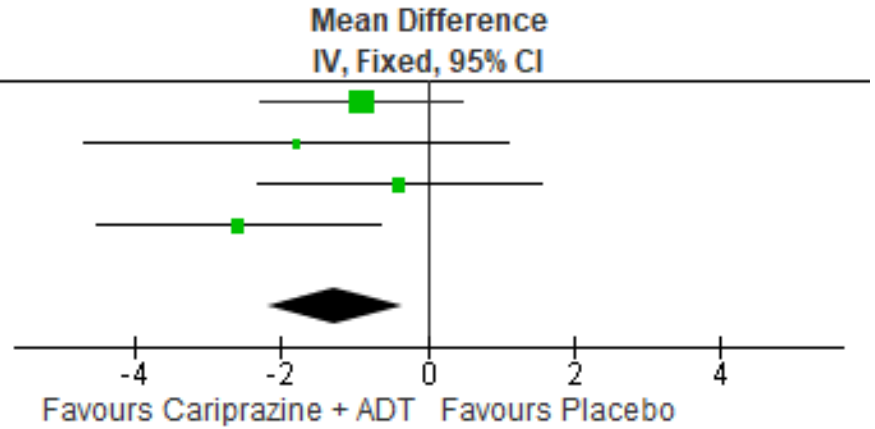
Response

- 5 RCTs, N = 3,068
- **GRADE: High**
  - Cariprazine showed rates of response (1% to 10% absolute change) that were typically not significant

Findings: Cariprazine vs. Placebo: Change in MADRS

Study or Subgroup	Cariprazine + ADT Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Durgam et al., 2016	-13.4	8.2614	273	-12.5	8.124	264	44.5%	-0.90 [-2.29, 0.49]
Fava et al. 2018	-9.8	9.3984	73	-8	9	81	10.1%	-1.80 [-4.71, 1.11]
Riesenberg 2023	-13.8	11.068	250	-13.4	10.8444	240	22.7%	-0.40 [-2.34, 1.54]
Sachs et al. 2023	-14.1	11.068	250	-11.5	11.0458	249	22.7%	-2.60 [-4.54, -0.66]
Total (95% CI)			**846**			**834**	**100.0%**	**-1.26 [-2.19, -0.34]**

Heterogeneity: Chi² = 2.98, df = 3 (P = 0.40); I² = 0%
Test for overall effect: Z = 2.68 (P = 0.007)

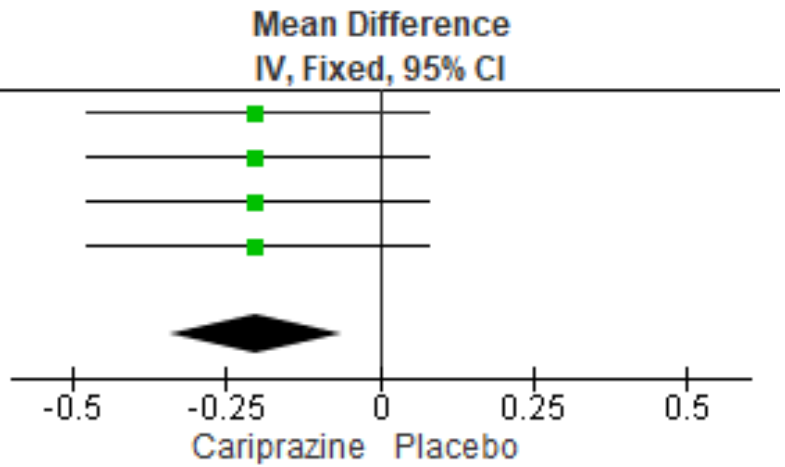


Findings: Cariprazine vs. Placebo: CGI-I

	Cariprazine			Placebo				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
Durgam et al., 2016	2.3	1.6523	273	2.5	1.6248	264	25.0%	-0.20 [-0.48, 0.08]
Earley et al. 2018	2.3	1.4526	211	2.5	1.4799	219	25.0%	-0.20 [-0.48, 0.08]
Fava et al. 2018	2.3	0.8544	73	2.5	0.9	81	25.0%	-0.20 [-0.48, 0.08]
Sachs et al. 2023	2.6	1.5811	250	2.8	1.578	249	25.0%	-0.20 [-0.48, 0.08]
Total (95% CI)			**807**			**813**	**100.0%**	**-0.20 [-0.34, -0.06]**

Heterogeneity: Chi² = 0.00, df = 3 (P = 1.00); I² = 0%

Test for overall effect: Z = 2.83 (P = 0.005)

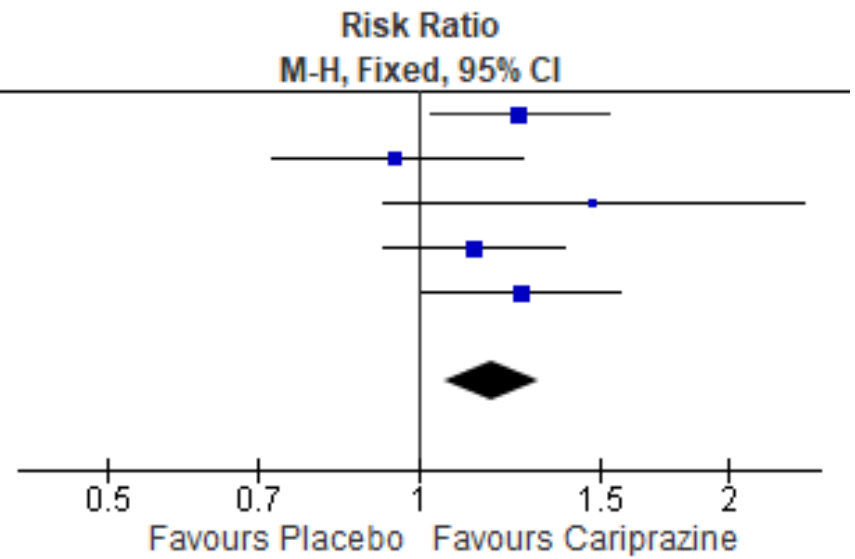


Findings: Cariprazine vs. Placebo: Response

Study or Subgroup	Cariprazine (1-2 mg/d) Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Durgam et al., 2016	131	273	101	264	26.7%	1.25 [1.03, 1.53]
Earley et al. 2018	71	267	72	258	19.1%	0.95 [0.72, 1.26]
Fava et al. 2018	28	73	21	81	5.2%	1.48 [0.93, 2.37]
Riesenberg 2023	115	250	101	249	26.3%	1.13 [0.93, 1.39]
Sachs et al. 2023	110	250	87	249	22.7%	1.26 [1.01, 1.57]
Total (95% CI)		**1113**		**1101**	**100.0%**	**1.18 [1.06, 1.31]**
Total events	455		382			

Heterogeneity: Chi² = 4.00, df = 4 (P = 0.41); I² = 0%

Test for overall effect: Z = 3.01 (P = 0.003)



Findings: Cariprazine vs. Placebo: Harms

BARS

- 5 RCTs, N = 3,068
- **GRADE: High**
  - Cariprazine showed modestly higher scores (increase in akathisia)

Change in body weight

- 5 RCTs, N = 3,068
- **GRADE: High**
  - Cariprazine typically showed 0.4 kg to 0.9 kg increase in body weight in the first 6 weeks of therapy

Olanzapine/fluoxetine

Findings: Olanzapine/fluoxetine vs. Placebo or Monotherapy: Efficacy

MADRS

- 5 RCTs, N = 2,077
- **GRADE: High**
  - Olanzapine/fluoxetine improved scores 3 to 5 points

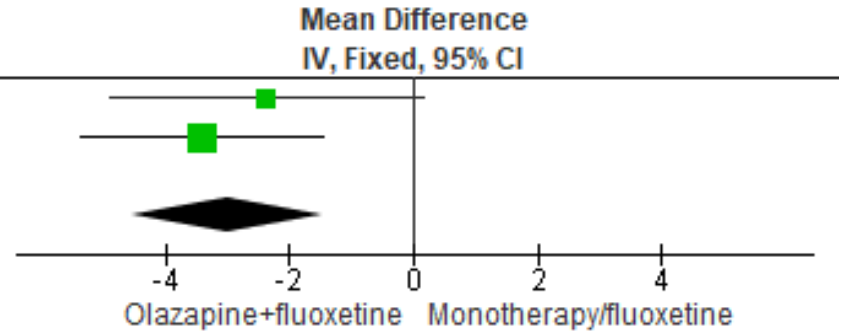
Response

- 4 RCTs, N = 1,633
- **GRADE: Moderate**
  - Olanzapine/fluoxetine showed inconsistent results ranging from 1% to 18% absolute difference

Findings: Olanzapine/fluoxetine vs. Placebo or Monotherapy: Change in MADRS

Study or Subgroup	Olazapine+fluoxetine Mean	SD	Total	Monotherapy/fluoxetine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Corya 2006	-14.06	9.1972	243	-11.7	8.8304	60	37.5%	-2.36 [-4.88, 0.16]
Thase 2007	-12.6	10.3	200	-9.2	9.7	206	62.5%	-3.40 [-5.35, -1.45]
Total (95% CI)			**443**			**266**	**100.0%**	**-3.01 [-4.55, -1.47]**

Heterogeneity: Chi² = 0.41, df = 1 (P = 0.52); I² = 0%
Test for overall effect: Z = 3.83 (P = 0.0001)

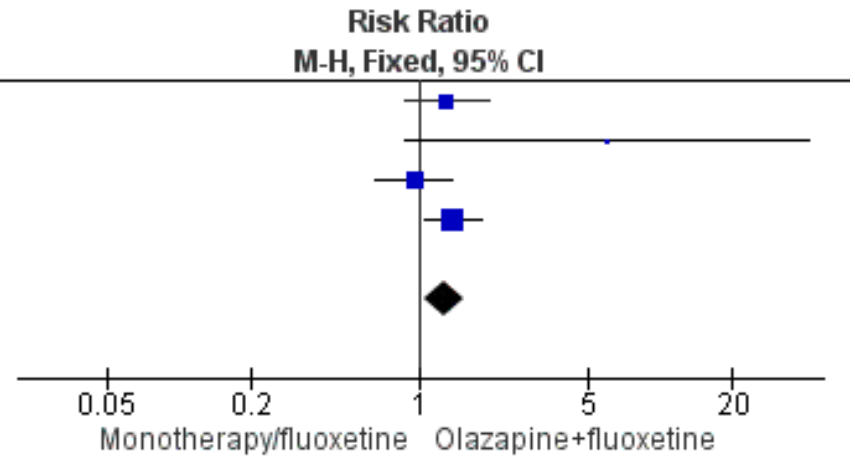


Findings: Olanzapine/fluoxetine vs. Placebo or Monotherapy: Response

	Olanzapine+fluoxetine		Monotherapy/fluoxetine			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Corya 2006	100	243	19	60	23.0%	1.30 [0.87, 1.94]
Shelton 2001	6	10	1	10	0.8%	6.00 [0.87, 41.21]
Shelton 2005	40	146	41	142	31.4%	0.95 [0.66, 1.37]
Thase 2007	80	198	60	203	44.8%	1.37 [1.04, 1.79]
Total (95% CI)		**597**		**415**	**100.0%**	**1.26 [1.04, 1.52]**
Total events	226		121			

Heterogeneity: Chi² = 5.14, df = 3 (P = 0.16); I² = 42%

Test for overall effect: Z = 2.34 (P = 0.02)



Findings: Olanzapine/fluoxetine vs. Placebo or Monotherapy: Harms

BARS

- 4 RCTs, N = 2,049
- **GRADE: Low**
  - Olanzapine/fluoxetine did not increase scores significantly during treatment

Change in body weight

- 4 RCTs, N = 2,049
- **GRADE: High**
  - Olanzapine/fluoxetine showed up to 6 kg increase in body weight at the start of therapy

Olanzapine vs. Aripiprazole vs. Lithium

Findings: Olanzapine vs. Aripiprazole vs. Lithium: Efficacy

HAM-D17

- 1 RCT, N = 30
- **GRADE: Very low**
  - There was no significant difference between therapies at week 4

Quetiapine vs. Placebo

Findings: Quetiapine vs. Placebo: Efficacy

MADRS

- 5 RCTs, N = 1,159
- **GRADE: Moderate**
  - MADRS scores typically improved 3 points during initial treatment; significance was inconsistent

CGI-I

- 6 RCTs, N = 1,253
- **GRADE: High**
  - Modest 1 point improvement in CGI-I scores

Response

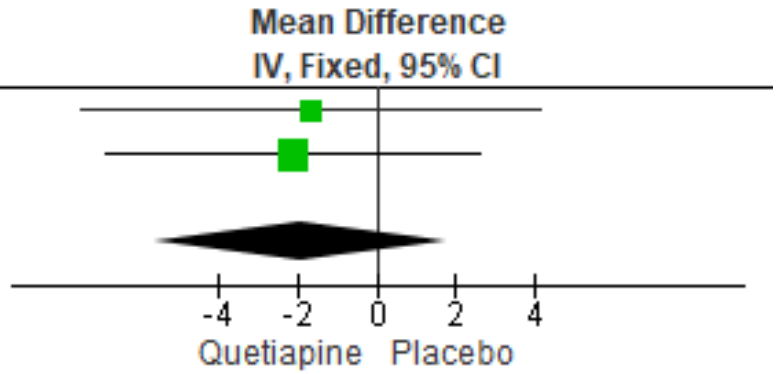
- 4 RCTs, N = 1,083
- **GRADE: High**
  - Quetiapine showed consistently higher rates of response (10% to 13% absolute change)

Findings: Quetiapine vs. Placebo: Change in MADRS

	Quetiapine			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Quante 2013	-14.28	10.95	19	-12.63	6.28	17	40.3%	-1.65 [-7.41, 4.11]
Ravindran 2022	-11.72	8.4031	48	-9.62	11.0378	28	59.7%	-2.10 [-6.83, 2.63]
Total (95% CI)			**67**			**45**	**100.0%**	**-1.92 [-5.57, 1.74]**

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² = 0%

Test for overall effect: Z = 1.03 (P = 0.30)

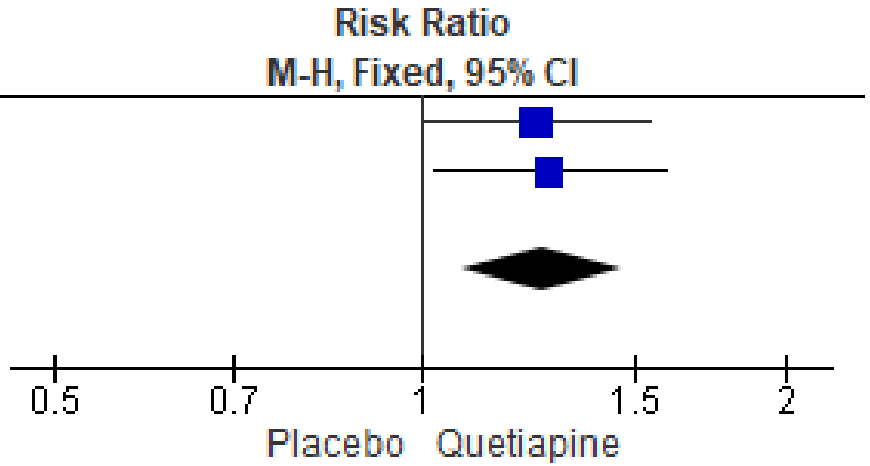


Findings: Quetiapine vs. Placebo: Response

Study or Subgroup	Quetiapine Events	Quetiapine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bauer 2009	93	161	74	160	52.0%	1.25 [1.01, 1.55]
El-Khalili 2010	88	150	68	148	48.0%	1.28 [1.02, 1.59]
Total (95% CI)		**311**		**308**	**100.0%**	**1.26 [1.08, 1.47]**
Total events	181		142			

Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² = 0%

Test for overall effect: Z = 2.98 (P = 0.003)



Findings: Quetiapine vs. Placebo: Harms

BARS

- 2 RCTs, N = 560
- **GRADE: Low**
  - No significant differences were reported

Change in body weight

- 7 RCTs, N = 1,329
- **GRADE: High**
  - Quetiapine typically showed 1 kg increase in body weight in the first 6 weeks of therapy

Quetiapine vs. Lithium

Findings: Quetiapine vs. Lithium: Efficacy

MADRS

- 2 RCTs, N = 708
- **GRADE: Low**
  - Quetiapine showed a significant improvement in MADRS in 1 study and no difference in 1 study

CGI-I

- 2 RCTs, N = 708
- **GRADE: Low**
  - Quetiapine showed a significant improvement in CGI-I in 1 study and no difference in 1 study

Response

- 1 RCT, N = 688
- **GRADE: Very low**
  - There was no difference between groups, with both reporting high response rates

Findings: Quetiapine vs. Lithium: Harms

Change in body weight

- 1 RCT, N = 688
- **GRADE: Low**
  - More participants reported weight gain as an AE in the quetiapine group

Risperidone

Findings: Risperidone vs. Placebo: Efficacy

MADRS

- 4 RCTs, N = 781
- **GRADE: Low**
  - MADRS scores typically improved 1 to 7 points during initial treatment

HAM-D17

- 4 RCTs, N = 841
- **GRADE: Low**
  - Inconsistent improvements in HAM-D17 scores

Response

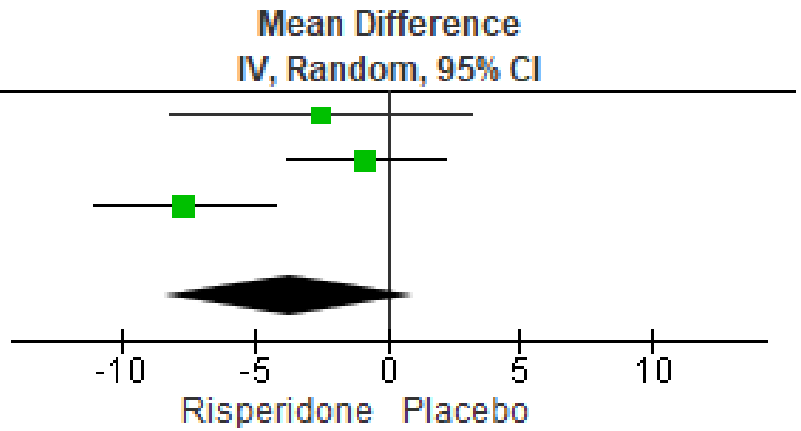
- 2 RCTs, N = 368
- **GRADE: Moderate**
  - Risperidone showed high rates of response (15% to 22% absolute change)

Findings: Risperidone vs. Placebo: Change in MADRS

Study or Subgroup	Risperidone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Alexopoulos 2008	-12.3	11.4	32	-9.8	11.5	31	26.9%	-2.50 [-8.16, 3.16]
Rapaport 2006	-11.2	12.6	122	-10.4	11.2	119	37.3%	-0.80 [-3.81, 2.21]
Reeves 2008	-22.09	3.29	12	-14.44	4.81	11	35.8%	-7.65 [-11.05, -4.25]
Total (95% CI)			**166**			**161**	**100.0%**	**-3.71 [-8.41, 1.00]**

Heterogeneity: $Tau^2 = 13.09$; $Chi^2 = 8.93$, df = 2 (P = 0.01); $I^2 = 78\%$

Test for overall effect: Z = 1.55 (P = 0.12)

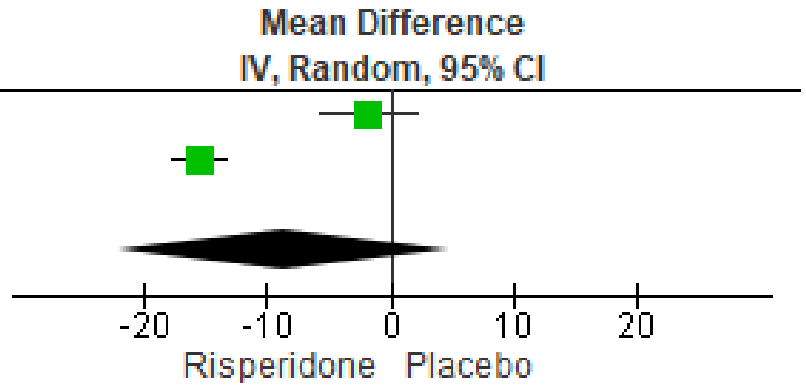


Findings: Risperidone vs. Placebo: Change in HAM-D17

	Risperidone			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Alexopoulos 2008	-8.3	7.9	32	-6.5	7.9	31	49.3%	-1.80 [-5.70, 2.10]
Rapaport 2006	-7.6	8.8	122	7.9	8.1	119	50.7%	-15.50 [-17.63, -13.37]
Total (95% CI)			**154**			**150**	**100.0%**	**-8.75 [-22.18, 4.67]**

Heterogeneity: $Tau^2 = 91.27$; $Chi^2 = 36.45$, df = 1 ($P < 0.00001$); $I^2 = 97\%$

Test for overall effect: $Z = 1.28$ ($P = 0.20$)



Findings: Risperidone vs. Placebo: Harms

BARS

- 2 RCTs, N = 460
- **GRADE: High**
  - Risperidone did not significantly worsen BARS scores

Change in body weight

- 5 RCTs, N = 865
- **GRADE: High**
  - More participants in the risperidone group reported weight gain as an AE

Ziprasidone

Findings: Ziprasidone vs. Placebo: Efficacy

MADRS

- 1 RCT, N = 64
- **GRADE: Very low**
  - MADRS scores improved 4 points (*P* = not significant)

CGI-I

- 2 RCTs, N = 203
- **GRADE: Moderate**
  - Ziprasidone showed improvement in 1 study and no improvement in 1 study

HAM-D17

- 2 RCTs, N = 203
- **GRADE: Moderate**
  - Ziprasidone showed improvement in 1 study and no improvement in 1 study

Findings: Ziprasidone vs. Placebo: Harms

BARS

- 1 RCTs, N = 64
- **GRADE: Very low**
  - No clinically relevant changes were reported

Ongoing Studies

Ongoing Studies (1 of 2)

- We identified 13 ongoing studies evaluating SGAs as adjuvant therapy for MDD, including:
  - 2 studies of aripiprazole
    - Comparators: bupropion, venlafaxine, escitalopram
    - Sample size: 252 to 278
    - Estimated completion: Apr 2021 to Dec 2025
  - 5 studies of brexpiprazole
    - Comparators: placebo, citalopram, escitalopram
    - Sample size: 122 to 1,149
    - Estimated completion: Apr 2021 to Apr 2029
  - 2 studies of cariprazine
    - Comparator: placebo
    - Sample size: 752 to 759
    - Completion: Sep 2021

Ongoing Studies (2 of 2)

- We identified 13 ongoing studies evaluating SGAs as adjuvant therapy for MDD including the following:
  - 3 studies of lumateperone
    - Comparator: placebo
    - Sample size: 470 to 760
    - Estimated completion: Feb 2024 to May 2024
  - 1 study of quetiapine
    - Comparator: amantadine, pramipexole
    - Sample size: 150
    - Completion: Sep 2024

Discussion

Discussion

- SGAs are a guideline-recommended addition to ADT in patients with treatment-resistant depression who have failed adequate trials of pharmacotherapy
- Most agents showed a 2 to 3–point improvement in MADRS scores during the first 6 to 8 weeks of therapy
- Response rates were inconsistent overall
- Movement AEs were typically reported with slightly higher BARS and AIMS scores, but it is not known if these would improve with continued therapy
- Weight gain is a significant concern with these agents, and it was consistently reported

Discussion

- GRADE ratings were generally *high* to *moderate* with consistent results seen between study groups with aripiprazole and brexpiprazole
  - Clinical efficacy debatable
- GRADE ratings were more variable for other therapies
- Limitations
  - Short study durations (5 to 8 weeks)
  - Lack of head-to-head studies
  - Lack of long-term follow-up

Questions?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