Review

Efficacy and Tolerability of Combination Treatments for Major Depression: Antidepressants plus Second-Generation Antipsychotics vs. Esketamine vs. Lithium

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Abstract

Background: Successful treatment of major depressive disorder (MDD) can be challenging, and failures ("treatment-resistant depression" [TRD]) are frequent. Steps to address TRD include increasing antidepressant dose, combining antidepressants, adding adjunctive agents, or using nonpharmacological treatments. Their *relative* efficacy and tolerability remain inadequately tested. In particular, the value and safety of increasingly employed second-generation antipsychotics (SGAs) and new esketamine, compared to lithium as antidepressant adjuncts remain unclear.

Methods: We reviewed randomized, placebo-controlled trials and used random-effects meta-analysis to compare odds ratio (OR) versus placebo, as well as numbers-needed-to-treat (NNT) and to-harm (NNH), for adding SGAs, esketamine, or lithium to antidepressants for major depressive episodes.

Results: Analyses involved 49 drug-placebo pairs. By NNT, SGAs were more effective than placebo (NNT = 11 [CI: 9–15]); esketamine (7 [5–10]) and lithium (5 [4–10]) were even more effective. Individually, aripiprazole, olanzapine+fluoxetine, risperidone, and ziprasidone all were more effective (all NNT < 10) than quetiapine (NNT = 13), brexpiprazole (16), or cariprazine (16), with overlapping NNT CIs. Risk of adverse effects, as NNH for most-frequently reported effects, among SGAs versus placebo was 5 [4–6] overall, and highest with quetiapine (NNH = 3), lowest with brexpiprazole (19), 5 (4–6) for esketamine, and 9 (5–106) with lithium. The risk/benefit ratio (NNH/NNT) was 1.80 (1.25–10.60) for lithium and much less favorable for esketamine (0.71 [0.60–0.80]) or SGAs (0.45 [0.17–0.77]).

Conclusions: Several modern antipsychotics and esketamine appeared to be useful adjuncts to antidepressants for acute major depressive episodes, but lithium was somewhat more effective and better tolerated.

Limitations: Most trials of adding lithium involved older, mainly tricyclic, antidepressants, and the dosing of adjunctive treatments were not optimized.

Keywords
Antidepressants, antipsychotics, combination, depression, efficacy, esketamine, lithium

Introduction

Major depressive disorder (MDD) is a highly prevalent, episodic, or sometimes chronic illness associated with potentially severe functional impairment, co-occurring psychiatric and general medical morbidity, and excess mortality from suicide as well as from general medical conditions (Baldessarini and Tondo, 2020; Celano et al., 2018; Seligman and Nemeroff, 2015). The lifetime prevalence of MDD is approximately 4%–14% of the general population and mixed features are present in a quarter of patients with MDD (Ferrari et al., 2013; Tondo et al., 2018; Vázquez et al., 2018; Zimmermann et al., 2009). Major mood disorders generally produce high illness burdens, with substantial risks of sustained disability (Ferrari et al., 2013; World Health Organization, 2012).

Modern antidepressants, with or without psychotherapy, are the leading form of treatment provided to MDD patients (Baldessarini, 2013; Bauer et al., 2013; Kennedy et al., 2016). However, response rates with commonly employed antidepressants for acute episodes of major depression are moderate (40%–60%), and remission rates are even lower (30%–45%) (Baldessarini, 2013; Rush et al., 2006; Yuan et al., 2020). Moreover, long-term levels of treatment-unresponsive depression in MDD and bipolar disorder (BD) are surprisingly high and typically involve more than 40% of the time in follow-up, despite treatment by community standards (Forte et al., 2015). The limited efficacy of antidepressant therapy, with correspondingly prevalent "treatment-resistant" depression (TRD), encourages clinical trials of alternatives, including increased doses of antidepressants, changing to different antidepressants, adding other drugs, or use of nonpharmacological (psychological and physical)

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treatments (Bauer et al., 2013; Davies et al., 2019; MacQueen et al., 2017; Milev et al., 2016; Parikh et al., 2009). Particularly striking is the relatively infrequent use of lithium in acute unipolar depression, despite its prolonged clinical acceptance and extensive support for use in nonbipolar major depression, particularly as an adjunct to antidepressants, in addition to representing a fundamental treatment for BD (Bauer et al., 2013; Kennedy et al., 2016; Undurraga et al., 2019). Also, addition of second-generation antipsychotic drugs (SGAs) to antidepressants has been increasing (Mulder et al., 2018), and esketamine is emerging as a novel, rapidly acting agent that can be added safely to antidepressants (Bahji et al., 2020, 2021).

Despite extensive clinical experience in the use of adjunctive treatments with antidepressants, greater clarity is required regarding the relative efficacy and tolerability of specific drug combinations and their doses for major depression. This need led us to evaluate trials testing short-term efficacy and tolerability of a currently prevalent option: SGAs, and their comparison with adjunctive esketamine as another innovative option, and with lithium as one of the oldest such adjunctive options (Haddad et al., 2015; Undurraga et al., 2019). Our assessments and comparisons are based on meta-analytic estimates of odds ratio (OR) as well as number-needed-to-treat (NNT) to indicate efficacy, and number-needed-to-harm (NNH) arising from commonly clinically encountered adverse effects. NNT and NNH are convenient and clinically readily interpretable measures that also can express relative risk-benefit relationships as the NNH/NNT ratio (Citrome and Ketter, 2013)].

Methods

Aims and eligibility criteria

We carried out a systematic review and meta-analysis and prepared this report adhering the preferred reporting items for systematic reviews and meta-analyses (PRISMA) (Liberati et al., 2009). We limited inclusion to peer-reviewed reports of randomized, nominally double-blinded, short-term ($\leqslant$12 weeks), placebo-controlled trials of selected agents of interest, including SGAs (those encountered were: aripiprazole, brexpiprazole, cariprazine, olanzapine+fluoxetine, risperidone, quetiapine, or ziprasidone; all inhibitors of serotonin 5-HT_2 and dopamine D_2 receptors), or intranasal esketamine, for comparison with lithium (usually as the carbonate), all combined with standard antidepressants to treat mainly unipolar major depressive episodes in adults diagnosed by modern criteria. We excluded reports involving special populations, such as juveniles, the elderly, or persons with major general medical or neurological illnesses.

Information sources and search

We systematically searched research literature in three electronic databases (PubMed, Google Scholar, and Medline) through October 2020 with combinations of the search terms: "major depression," "controlled," "randomized," "clinical trial," and "efficacy" (Appendix 1). We also examined previously published, partially relevant, systematic reviews (Bahji et al., 2020, 2021; Nelson and Papakostas, 2009; Ruberto et al., 2020; Spielmans et al., 2013; Undurraga et al., 2019) and references identified in them.

Of 4631 initially identified potential studies based on review of titles and abstracts, 124 required more detailed examination by two coauthors (GHV and RJB), resulting in 43 trials (with 49 drug-placebo pairs) meeting study inclusion criteria (Appendix Figure A1).

Summary measures

To combine the results of studies, we used a random-effects meta-analysis to pool effect sizes to obtain OR with 95% confidence intervals (CI), based on previously described methods (Bahji et al., 2020). We measured heterogeneity using the I^2 statistic (Higgins and Thompson, 2002). Most identified studies defined "response" as at least a 50% reduction in scores with standardized depressive symptom rating-scales, commonly the Hamilton depression rating scale [$HDRS_{17}$] or Montgomery-Åsberg Depression Rating Scale [MADRS]) (Hamilton, 1960; Montgomery and Åsberg, 1979). We summarized response rates using pooled ORs and their CIs.

We also computed initial depression severity ratings as the percentage of maximum possible scale scores (52 with $HDRS_{17}$, 60 with MADRS), and tested for their similarity between subjects randomized to active treatments versus to placebo, using paired-*t* tests.

In addition to response rates, clinical efficacy of individual agents and drug types was expressed semi-quantitatively as the estimated "NNT" (with CI), computed as the reciprocal of meta-analytically pooled differences in proportions of patients responding to an active drug versus placebo. NNT indicates the approximate number of patients treated to encounter a patient with superior benefit with a test treatment over a control condition (smaller NNT demonstrating greater efficacy), typically based on response rates with a drug versus with placebo.

To assess the acceptability and tolerability of treatments, we used NNH, which is the reciprocal of differences in proportions of patients reporting a common adverse effect with drug versus placebo; larger NNH values indicate greater tolerability (Andrade, 2015). The most prevalent adverse effects with antipsychotics were excessive sedation or somnolence, weight gain, extrapyramidal neurological symptoms, and akathisia; with intranasal esketamine the most commonly noted adverse effect was dizziness; and with lithium, tremor. NNT and NNH values for individual drugs and drug types were computed by random-effects meta-analysis and reported with 95% CI. They were compared statistically by contingency tables (χ^2) based on pooled responder rates and pooled rates of experiencing specified adverse effects.

Finally, we computed the *likelihood to be harmed or helped* (LHH) as the ratio of NNH to NNT (Citrome and Ketter, 2013). LHH reflects the balance between harm and benefits (risk/benefit ratio) and is reported for each drug and drug type for which data were available. Other measures are reported as means with 95% CI. Statistical significance required two-tailed $p < 0.05$. Analyses employed commercial software: *Statview.5* (SAS Institute, Cary, NC, USA) for spreadsheets, and *R Studio* (RStudio PBC, Boston, MA, USA) and *Stata.13* (StataCorp, College Station, TX, USA) for analyses.

Results

Overall findings

The PRISMA-guided process of selecting reports for inclusion is summarized in Appendix Figure A1. Of the 49 included trials (from 43 reports), four (with SGAs) involved more than one

drug-arm, yielding 28 trials for SGAs, 14 for lithium carbonate, and 7 for intranasal esketamine, for a total of 49 drug-placebo pairs.

A total of 8104 subjects were included in the 28 add-on SGA trials: 4030 randomized to combination with an SGA, and 4074 (3008 unique participants owing to repeated use of some controls) with added placebo. Trial-duration averaged 7.07 (6.49–7.65) weeks, subject-age averaged 44.7 (44.3–45.1) years, and 67.2% (67.1–67.3) of participants were women (Appendix Table A1). Mean baseline depression severity ratings, expressed as percentage of maximum attainable score, ranked: 51.5 (44.7–47.4) with lithium, 46.0 (44.7–47.4) with SGAs, and 37.6 (36.3–47.4) with esketamine. These initial scores differ highly significantly (overall $t=3.68$, $p<0.0001$), and each Scheffé post-hoc pairwise comparison also differs significantly (lithium vs. esketamine, $p<0.0001$; esketamine vs. SGA, $p=0.001$; lithium vs. SGA, $p=0.04$).

In the seven trials for intranasal esketamine as an add-on to antidepressant treatment, there were 1287 subjects: 711 randomized to added esketamine and 576 to added placebo. Trial duration was 4 weeks for all trials of esketamine, subject-age averaged 46.0 (40.1–46.0) years, and 63.0% (55.5–76.3) of participants were women (Appendix Table A2).

Of the 14 trials for lithium carbonate as an add-on to antidepressant treatment, there were 640 subjects: 292 randomized to added lithium and 348 to added placebo. Trial duration averaged 3.4 (2.0–4.8) weeks, subject-age averaged 43.7 (40.0–47.0) years, and 63.0% (55.5–76.3) of participants were women (Appendix Table A3).

Meta-analyses

Random-effects meta-analysis of trials of adding SGAs versus placebo to antidepressants yielded highly significant superiority of SGAs overall (OR = 1.59 [CI: 1.44–1.75]; $z=9.16$, $p<0.0001$; Figure 1(a)). The efficacy of intranasal esketamine was intermediate between SGAs and lithium (OR = 1.94 [1.52–2.46]; $z=4.98$, $p<0.0001$; Figure 1(b)), and the efficacy of lithium was highest (OR = 2.22 [1.44–3.43]; $z=3.59$, $p=0.0003$; Figure 1(c)).

NNT

NNT values for *response* among individual drugs or types (Table 1) did not differ significantly (overlapping CIs), but tended to be lower (more favorable) with lithium (NNT = 5 [4–10]) than with esketamine (NNT = 7 [5–10]) or SGAs overall (11 [9–15]). NNT among particular SGAs ranked: risperidone (6 [3–13]) = olanzapine/fluoxetine (which includes an antidepressant; 6 [4–19]) ⩽ ziprasidone (7 [3–∞]) ⩽ aripiprazole (9 [5–24]) ⩽ cariprazine (16 [8–52]) = brexpiprazole (16 [10–34]; Table 1). Based on responder rates, lithium was significantly superior to SGAs ($\chi^2=19.6$, $p<0.0001$), as was esketamine ($\chi^2=30.9$, $p<0.0001$), whereas lithium and esketamine did not differ significantly ($\chi^2=0.340$, $p=0.561$).

NNH

NNH for lithium was highest (lowest risk) at 9 [5–106], and greater than with intranasal esketamine (5 [4–6]) or all SGAs pooled (5 [4–6]). For individual SGAs, NNH ranged from 19 with brexpiprazole to 3 with quetiapine (Table 2). Based on adverse event rates, lithium was safer than either SGAs or esketamine ($\chi^2=1567$ and 158, respectively; both $p\leqslant 0.0001$), and risk was lower with esketamine than with SGAs ($\chi^2=13.0$, $p=0.0003$).

In addition, the LHH or risk/benefit ratio (NNH/NNT) was more favorable (larger) with lithium (LHH = 1.50 [1.08–3.34] than with intranasal esketamine (LHH = 0.71 [0.60–0.80]) or SGAs-combined (LLH = 0.45 [0.17–0.77]; Table 2), with nonoverlapping CIs.

Discussion

This systematic review compared efficacy (as OR vs. placebo in random-effects meta-analyses and as NNT) and tolerability (as NNH) and their risk/benefit ratio (NNH/NNT, or LHH) in placebo-controlled, randomized, add-on trials of SGAs, intranasal esketamine, or lithium to supplement standard antidepressants. Literature searching yielded 43 peer-reviewed reports meeting study criteria, with 49 drug-placebo pairs (Figure 1).

SGAs overall were more effective than placebo (OR = 1.59 [1.44–1.75]; NNT = 11 [9–15]), but esketamine (OR = 1.96 [1.55-2.50]; NNT = 7 [5–10]) and lithium (OR = 2.04 [1.42–2.93]; NNT = 5 [4–10]) were even more effective. Individually, compared to placebo, aripiprazole, olanzapine + fluoxetine, risperidone, and ziprasidone were more effective than placebo in attaining an antidepressant response (all NNT < 10), and more so than quetiapine (NNT = 13), brexpiprazole (NNT = 16), or cariprazine (NNT = 16). However, the CIs of NNTs for individual added SGAs treatments overlapped.

Apparent risk of adverse effects, as NNH (higher value with lower risk) for most frequently reported effects among SGAs versus placebo, was highest with quetiapine (NNH = 3) and lowest with brexpiprazole (NNH = 19). In addition, the NNH was lower (higher risk) with intranasal esketamine (NNH = 5 [4–6] and all SGAs-pooled (5 [4–6]) than with lithium (9 [5–106]). The benefit/risk ratio (NNH/NNT, or LHH; Table 2) was 1.50 [1.08–3.34] for lithium and much lower, or less favorable, with intranasal esketamine (0.71 [0.60–0.80]) and all SGAs (0.45 [0.17–0.77]).

These findings support the efficacy of SGAs, intranasal esketamine, and lithium over placebo in supplementing antidepressant treatment of acute major depression in adults. However, the trials included are heterogeneous, and computed values of NNT for individual SGAs had overlapping CIs, limiting their potential value in guiding recommendations regarding which drug should be used as a first choice. Moreover, initial depression severity ratings normalized as the percentage of maximum scale scores differed significantly and ranked: lithium (51.1%) > SGAs (46.0%) > esketamine (37.6%). The same order was found regarding efficacy as OR in meta-analyses (Figure 1) and as NNT (Table 1). This ranking may suggest preferential efficacy with higher initial depression severity, favoring lithium, or possibly an artifact of contrasts between higher initial to end-point depression ratings.

We also found similar results regarding tolerability as NNH, ranking: lithium ⩾ intranasal esketamine ⩾ SGAs (Table 2). Tolerability and efficacy is essential in deciding which treatment should be used, as adverse effects can reduce subjective well-being and treatment-adherence and adversely affect treatment outcomes (Solmi et al., 2017). Use of SGAs can lead to a range of adverse effects, including excessive sedation, akathisia, and risks of weight gain and adverse cardiometabolic effects with some SGAs (Baldessarini, 2013; Centorrino et al., 2012; Gierisch et al., 2014; Solmi et al., 2017). Use of intranasal esketamine at

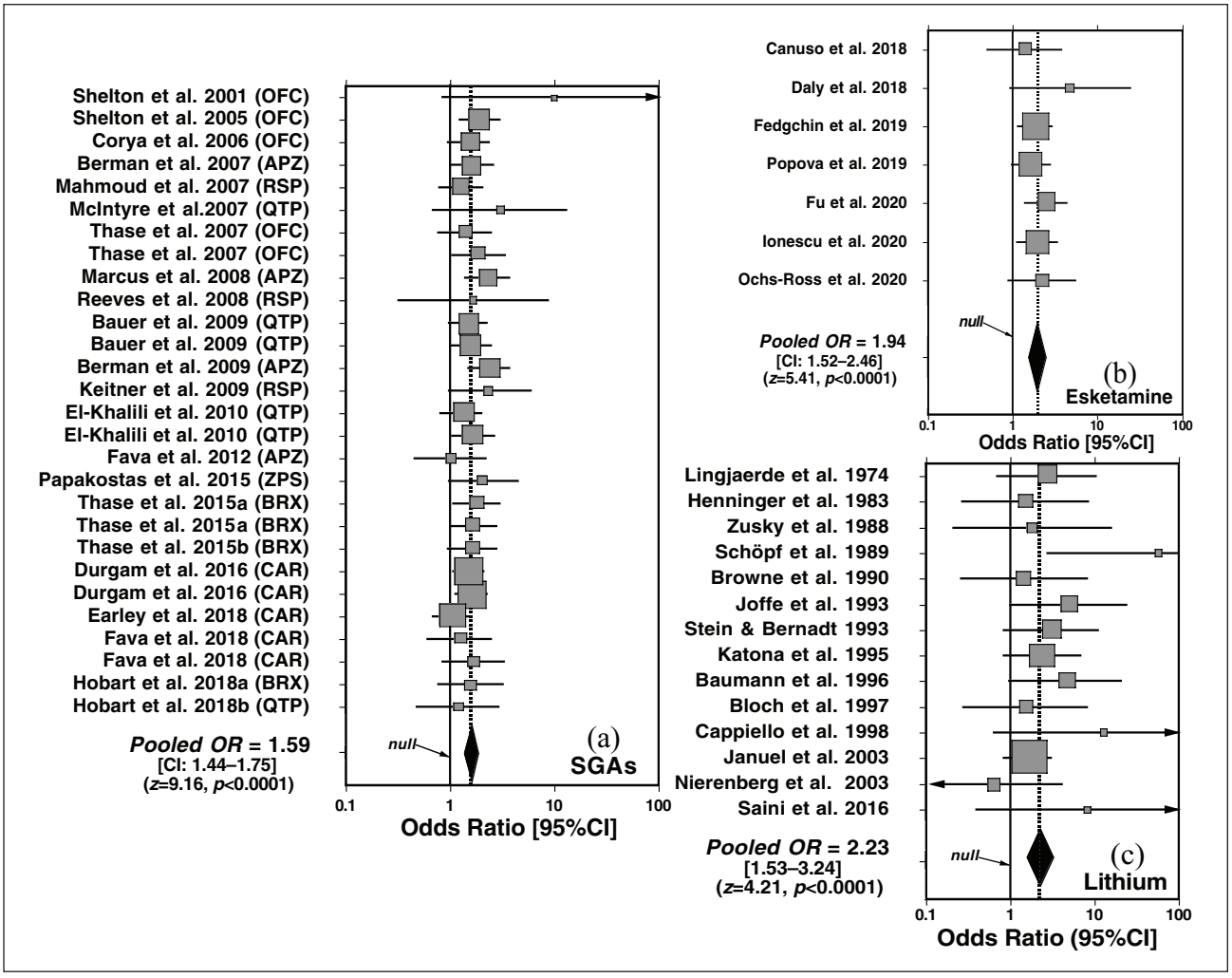

Figure 1. Forest plots of random-effects meta-analyses for clinical trials testing the efficacy of supplementing antidepressants with active agents or placebo for major depression: (a) second-generation antipsychotics (SGAs, 28 trials), (b) intranasal esketamine (7 trials), or (c) lithium carbonate (13 trials). SGAs tested were: APZ, aripiprazole; BRX, brexpiprazole; CAR, cariprazine; OFC, olanzapine+fluoxetine combination; QTP, quetiapine; RSP, risperidone; ZPS, ziprasidone. Adding all three types of active treatments were much more effective than adding placebo: (a) SGAs: pooled OR=1.59 [CI: 1.44–1.75]; *z*-score=9.16, $p < 0.0001$; (b) esketamine: pooled OR=1.85 [1.45–2.35]; *z*-score=4.98, $p < 0.0001$; Lithium: pooled OR=2.12 [1.46–3.09]; $z = 3.92$, $p < 0.0001$. Heterogeneity ratings (I^2) all were <1.0%.

Table 1. Efficacy of lithium or second-generation antipsychotics (SGAs) versus placebo (PBO) added to antidepressants for major depression.

Treatment	Studies (*n*)	Responders (%)		Response measures [95%CI]	
		Drug	Placebo	OR	NNT
Lithium	14	148/292 (50.7)	111/348 (32.0)	2.04 [1.42–2.93]	5 [4–10]
Esketamine	7	346/711 (48.7)	188/576 (32.6)	1.96 [1.55–2.50]	7 [5–10]
All SGAs	28	1516/4030 (37.6)	1100/4074 (27.0)	1.59 [1.44–1.75]	11 [9–15]
Risperidone	3	104/211 (49.3)	53/172 (30.8)	2.12 [1.39–3.25]	6 [4–13]
Olanzapine/fluoxetine	5	255/593 (43.0)	163/541 (30.1)	1.72 [1.27–2.34]	6 [4–19]
Ziprasidone	1	25/71 (35.2)	14/68 (20.6)	2.10 [0.98–4.50]	7 [3–∞]
Aripiprazole	4	216/608 (35.5)	151/709 (21.3)	1.89 [1.38–2.57]	9 [5–24]
Quetiapine	6	369/745 (49.5)	304/843 (36.1)	1.50 [1.21–1.86]	13 [8–42]
Cariprazine	5	390/967 (40.3)	315/952 (33.1)	1.38 [1.14–1.66]	16 [8–52]
Brexpiprazole	4	157/790 (19.9)	100/789 (12.7)	1.70 [1.29–2.24]	16 [10–34]

Data are ranked in ascending order of number-needed-to-treat (NNT).

Table 2. Relative risk of adverse events associated with second-generation antipsychotics (SGAs, esketamine or lithium versus placebo (PBO) added to antidepressants for major depression.

Treatment	Trials (n)	Adverse event	Adverse events/person (%)		NNH [95%CI]	LHH (NNH/NNT) [95%CI]
			Drug	PBO		
Lithium	14	Tremor	120/140 (80.5)	99/142 (69.7)	9 [5–106]	1.80 [1.25–10.60]
Esketamine	7	Dizziness	216/736 (22.4)	56/576 (7.6)	5 [4-6]	0.71 [0.60–0.80]
All SGAs	25	Various	969/4178 (23.2)	202/3311 (6.10)	5 [4–6]	0.45 [0.17–0.77]
Brexpiprazole	4	Akathisia	83/1032 (8.04)	21/819 (2.56)	19 [14–29]	1.19 [1.04–1.66]
Olanzapine/fluoxetine	5	Weight-gain >10%	109/584 (18.7)	4/537 (0.74)	9 [5–20]	1.50 [1.08–3.34]
Cariprazine	3	Akathisia	131/962 (13.6)	17/605 (2.8)	9 [7–12]	0.56 [0.30–0.80]
Risperidone	2	Sedation/somnolence	15/211 (7.11)	10/175 (5.71)	5 [4–6]	0.83 [0.36–1.00]
Ziprasidone	1	Sedation/somnolence	24/71 (33.8)	8/68 (11.7)	5 [3–11]	0.71 [0.29–0.96]
Aripiprazole	4	EPS/akathisia	243/662 (36.7)	90/769 (11.7)	4 [3–5]	0.44 [0.14–0.79]
Quetiapine	6	Sedation/somnolence	364/656 (55.5)	52/338 (15.4)	3 [2–3]	0.23 [0.05–0.54]

Data are ranked by descending NNH.
CI: confidence interval; EPS: extrapyramidal signs or symptoms; LLH: likelihood of help or harm or risk/benefit ratio (NNH/NNT); NNH: number-needed-to-harm; NNT: number needed to treat; PBO: placebo; SGA: second-generation antipsychotic.

approved doses can lead to other adverse events, including dizziness, dissociation, headaches, paraesthesia, nausea, vomiting, and somnolence, with even potential risks of psychosis at higher doses (Bahji et al., 2021). Of note, mean duration of lithium trials was shorter than for esketamine and SGAs; this difference may imply a faster antidepressant action with lithium, and might also limit appearance of side effects.

Lithium is effective for treating affective disorders with evidence of reduction of suicidal risk and mortality, but is underutilized (Baldessarini, 2013; Undurraga et al., 2019) especially in MDD. Concerns that limit the use of lithium include a narrow therapeutic index, with risks of intoxication at circulating concentrations only 2–3 times above therapeutic levels, as well as of adverse long-term effects on thyroid and renal function (Baldessarini, 2013). In addition, lithium salts have lacked commercial promotion as unpatentable minerals in competition with other treatments.

NNT is a convenient and clinically readily interpretable measure of therapeutic effect-size and may support comparisons of different treatments given under comparable conditions, but it has important limitations (Andrade, 2015; Mendes et al., 2017). In the present analyses, lithium yielded an NNT of 5 (4–10), indicating that approximately one out of five patients treated would respond to adding lithium to an antidepressant in comparison with adding placebo. Generally, small NNTs are preferable, although larger values (>10) may be acceptable if the outcome is the prevention of mortality or severe morbidity (Katsanos et al., 2015). Also, meaningful interpretation of NNT requires consideration of response rate: a relatively low response rate with an active treatment may be significantly superior to that with placebo, but not be clinically valuable. NNH and the risk/benefit ratio (NNH/NNT) are also subject to limitations, notably including the clinical significance of the adverse effect being considered.

Limitations

Most trials of adding lithium to antidepressants for major depressive episodes involved older, mainly tricyclic, antidepressants, and dosing of all reported adjunctive treatments were not optimized. We also found poor systematization of the adverse effect profile in some trials, especially involving lithium. Use of NNT and NNH to compare treatments is limited by the comparability of different trials and further limited by the rarity of desirable, head-to-head comparisons of different active treatments under identical conditions.

Conclusions

Based on meta-analyses to determine the OR and NNT, several modern drugs developed as antipsychotics as well as intranasal esketamine were effective as adjuncts to antidepressants for acute major depressive episodes, but lithium was somewhat more effective and better tolerated. The findings encourage clinical consideration of lithium as a particularly attractive adjunct in the treatment of major depression.

Declaration of conflicting interests

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Appendix

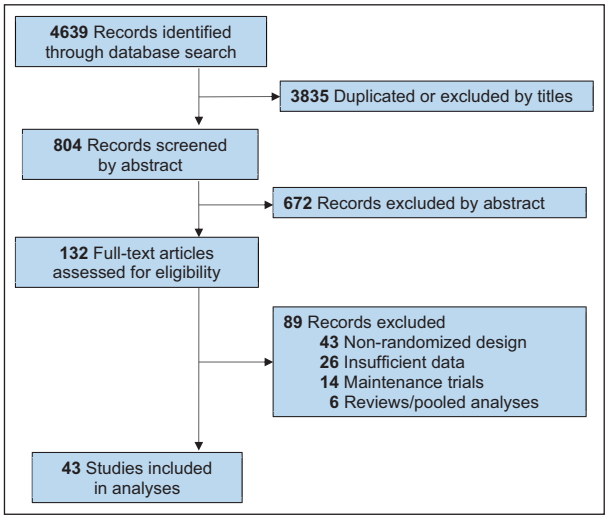

Figure A1. Flow-chart of selection of reports for inclusion in study, based on PRISMA recommendations (http://www.prisma-statement.org/PRISMAStatement/PRISMAStatement) to yield 39 reports (with 43 trials) included for analysis.

Table A1. Characteristics of second-generation antipsychotics (SGAs) vs. placebo (PBO) add-on trials for major depressive episodes.

Report	SGAs	ADs	Mean SGA dose (mg/day)	Subjects (*N*)		Mean age (years)	Female (%)	Time (weeks)	Failed AD trials	Ratings	Responders [*n* (%)]		Response OR
				SGA	PBO						SGA	PBO	
Shelton et al. (2001)	OFC	FLX	Flexible (13.5/52)	9	9	42	75	8	2 prior, 1 pros	MADRS	5 (55.6)	1 (11.1)	10.0
Shelton et al. (2005)	OFC	FLX/NRT	Flexible (8.5/35.6)	146	210	44	64	8	1 prior, 1 pros	MADRS	65 (44.5)	62 (29.5)	1.92
Corya et al. (2006)	OFC	FLX/VNX	Fixed (6, 12/25, 50)	243	119	46	72	12	11 prior, 1 pros	MADRS	105 (43.2)	40 (33.6)	1.50
Berman et al. (2007)	APZ	Various	Flexible (11.8)	184	178	45	63	6	1–3 prior, 1 pros	MADRS	62 (33.7)	42 (23.6)	1.65
Mahmoud et al. (2007)	RSP	Various	Flexible (1 or 2)	137	131	46	74	6	1 pros	HDRS	63 (46.0)	38 (29.0)	1.27
McIntyre et al. (2007)	QTP	Various	Flexible (182)	18	16	44	62	8	1 prior	HDRS	9 (50.0)	4 (25.0)	3.00
Thase et al. (2007)	OFC	FLX	Fixed (6, 12, 18/50)	101	102	44	60	8	1 prior, 1 pros	MADRS	37 (36.6)	30 (29.4)	1.39
Thase et al. (2007)	OFC	FLX	Fixed (6, 12, 18/50)	97	101	45	68	8	1 prior, 1 pros	MADRS	43 (44.3)	30 (29.7)	1.89
Marcus et al. (2008)	APZ	Various	Flexible (11.0)	191	190	44	70	6	1–3 prior, 1 pros	MADRS	62 (32.5)	33 (17.4)	2.29
Reeves et al. (2008)	RSP	Various	Flexible (1.2)	12	11	44	70	8	1 pros	MADRS	7 (58.3)	5 (45.4)	1.68
Bauer et al. (2009)	QTP	Various	Fixed (150 or 300)	167	163	45	68	6	1 prior	MADRS	93 (55.7)	75 (46.0)	1.47
Bauer et al. (2009)	QTP	Various	Fixed (150 or 300)	163	163	45	68	6	1 prior	MADRS	94 (57.7)	75 (46.0)	1.60
Berman et al. (2009)	APZ	Various	Flexible (13.9)	177	172	45	73	6	1–3 prior, 1 pros	MADRS	82 (46.3)	46 (26.7)	2.36
Keitner et al. (2009)	RSP	Various	Flexible (1.6)	62	30	45	57	4	1 pros	MADRS	34 (54.8)	10 (33.3)	2.43
El-Khalili et al. (2010)	QTP	Various	Fixed (150 or 300)	148	148	46	72	6	1 prior	MADRS	77 (52.0)	68 (46.0)	1.28
El-Khalili et al. (2010)	QTP	Various	Fixed (150 or 300)	150	148	46	72	6	1 prior	MADRS	88 (58.7)	68 (46.0)	1.67
Fava et al. (2012)	APZ	Various	Fixed (2–5)	56	169	45	65	8	1–3 prior, 1 pros	MADRS	10 (17.9)	30 (17.8)	1.01
Papakostas et al. (2015)	ZPS	sCTP	Flexible (98)	71	68	44	70	8	1 pros	HDRS	25 (35.2)	14 (20.6)	2.09
Thase et al. (2015a)	BRX	Various	Fixed (1 or 3)	211	203	46	68	6	1–3 prior, 1 pros	MADRS	49 (23.2)	29 (14.3)	1.81
Thase et al. (2015a)	BRX	Various	Fixed (1 or 3)	213	203	46	68	6	1–3 prior, 1 pros	MADRS	47 (22.1)	29 (14.3)	1.70
Thase et al. (2015b)	BRX	Various	Fixed (2)	175	178	45	70	6	1–3 prior, 1 pros	MADRS	41 (23.4)	28 (15.7)	1.64
Durgam et al. (2016)	CAR	Various	Fixed (1–2)	273	266	45	68	8	1 pros	MADRS	131 (48.0)	101 (38.0)	1.51
Durgam et al. (2016)	CAR	Various	Fixed (2–4.5)	271	266	45	73	8	1 pros	MADRS	134 (49.4)	101 (38.0)	1.60
Earley et al. (2018)	CAR	Various	Fixed (1.5–4.5)	269	258	44	65	8	1–2 prior, 1 pros	MADRS	75 (27.9)	71 (27.5)	1.02
Fava et al. (2018)	CAR	Various	Fixed (0.1–0.3)	76	81	46	52	8	1–2 prior, 1 pros	MADRS	23 (30.3)	21 (25.9)	1.24
Fava et al. (2018)	CAR	Various	Fixed (1–2)	73	81	44	51	8	1–2 prior, 1 pros	MADRS	27 (37.0)	21 (25.9)	1.68
Hobart et al. (2018a)	BRX	Various	Flexible (2.2)	191	205	43	74	6	1–3 prior, 1 pros	MADRS	20 (10.5)	14 (6.83)	1.60
Hobart et al. (2018b)	QTP-xr	Various	Fixed (150 or 300)	99	205	43	69	6	1–3 prior, 1 pros	MADRS	8 (8.08)	14 (6.83)	1.20
Totals/averages [95%CI]	–	–	–	3983	4074*	44.7 [44.3–45.1]	67.2 [67.1–67.3]	7.07 [6.49–7.65]	–	–	1516/3983 (38.1%) [36.6–39.6]	1100/4074 (27.0%) [25.6–28.4]	1.59 [1.44–1.75]

Data are derived from 28 trials in 22 reports. The pooled Response Ratio is based on pooled rates for SGAs/PBO (38.1%/28.9%). The mean response ratio = 1.57 [1.22–1.92], based on ratios in individual trials, but based on pooled counts of responders/subjects, the ratio is 1.41 (38.1%/27.0%), based on 1516/3983 = 38.1% with SGAs versus 1100/4074 = 27.0% with PBO. There are 28 SGA trials. OR was determined from random-effects meta-analysis. Of the 28 trials, 11 (39.3%) independently favored SGA over PBO significantly.

ADs: antidepressants; APZ: aripiprazole; BRX: brexpiprazole; CAR: cariprazine; FLX: fluoxetine; NRT: nortriptyline; OFC: olanzapine+fluoxetine combination; PBO: placebo; pros: prospective; QTP: quetiapine; Rem: remission; xr: extended release.

*Corrected for repeated use, the placebo total *N* = 3008.

Table A2. Characteristics of esketamine (sKet) versus placebo (PBO) add-on trials for major depressive episodes.

Study	sKet (nasal dose)	Age (years)	Females (%)	Subjects (*N*)		Responders (%)		Response OR
				sKet	PBO	sKet	PBO	
Canuso et al. (2018)	84 mg twice/week	35.9	65.2	35	31	24 (68.6)	19 (61.3)	1.38
Daly et al. (2018)	28–84 mg twice/week	45.4	57.0	34	33	8 (23.5)	2 (6.06)	4.77
Fedgchin et al. (2019)	56–84 mg twice/week	46.6	71.1	229	113	123 (53.7)	44 (38.9)	1.82
Popova et al. (2019)	56–84 mg twice/week	45.7	61.9	114	109	70 (61.4)	52 (47.7)	1.74
Fu et al. (2020)	84 mg twice/week	39.3	61.6	113	112	51 (45.1)	28 (25.0)	2.47
Ionescu et al. (2021)	84 mg twice/week	40.8	59.9	114	113	53 (46.5)	35 (31.0)	1.94
Ochs-Ross et al. (2020)	28–84 mg twice/week	70.0	62.0	72	65	17 (23.6)	8 (12.3)	2.20
Totals/averages [95%CI]	28–84 mg twice weekly	46.2 [35.9–56.5]	62.7 [58.6–66.8]	711	576	346/711 (48.7%) [44.9–52.4]	188/576 (32.6%) [28.8–36.6]	2.23 [1.53–3.24]

OR was determined from random-effects meta-analysis. Of the seven trials, three (42.9%) independently favored esketamine over placebo significantly.

Table A3. Characteristics of lithium versus placebo (PBO) add-on trials for major depressive episodes.

Study	ADs	Age (years)	Females (%)	Lithium dose	Duration (weeks)	Subjects (*N*)		Responders (%)		Response OR
						Lithium	Placebo	Lithium	Placebo	
Lingjærde et al. (1974)	TCAs	49	78	0.8–1.3 mM	6	20	25	8 (40.0)	5 (20.0)	2.67
Heninger et al. (1983)	TCAs, MIA	51	80	900–1200 mg/day (0.5–1.1 mM)	2	8	17	5 (62.5)	9 (52.9)	1.48
Zusky et al. (1988)	TCAs, MAOIs	45	81	900 mg/day	2	8	8	3 (37.5)	2 (25.0)	1.80
Schöpf et al. (1989)	TCAs	54	70	600–800 mg/day (0.6–0.8 mM)	1	14	13	9 (64.3)	0 (0.00)	57.0
Browne et al. (1990)	TCAs	42	59	900 mg/day	2	15	15	4 (26.7)	3 (20.0)	1.45
Joffe et al. (1993)	TCAs	37	55	900 mg/day	2	17	16	9 (52.9)	3 (18.8)	4.88
Stein and Bernadt (1993)	TCAs	47	79	250 mg/day	3	16	34	7 (43.8)	7 (20.6)	3.00
Katona et al. (1995)	FLX, LFP	40	57	800 mg/day (0.6–1 mM)	6	29	32	15 (51.7)	10 (31.3)	2.36
Baumann et al. (1996)	CTP	41	71	800 mg/day (0.5–0.8 mM)	1	10	32	6 (60.0)	8 (25.0)	4.50
Bloch et al. (1997)	DMI	47	55	0.7–1.0 mM	5	16	15	9 (56.3)	10 (66.7)	1.50
Cappiello et al. (1998)	DMI	40	66	900 mg/day	4	14	15	4 (28.6)	0 (0.0)	13.3
Januel et al. (2003)	CMI	44	62	750 mg/day	2	74	75	42 (56.8)	34 (45.3)	1.58
Nierenberg et al. (2003)	NRT	38	46	900 mg/day	6	18	17	2 (11.1)	3 (17.6)	0.58
Saini et al. (2016)	IMI	37	23	0.6–0.8 mM	4	20	20	20 (100.0)	17 (85.0)	8.20
Totals/averages [95%CI]	–	43.7 [40.6–46.8	63.0 [53.8–72.2]	0.6–1.3 mM	3.29 [1.57–5.01]	279	364	143/279 (51.3%) [45.2–57.3]	111/364 (30.5%) [25.8–35.5]	2.23 [1.53–3.24]

OR was determined from random-effects meta-analysis. Of the 14 trials, three (21.4%) significantly favored Li over placebo independently.