Safety and Tolerability of Antidepressant Co-treatment in Acute Major Depressive Disorder: A Systematic Review and Exploratory Meta-analysis

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BACKGROUND

- Response rate with initial antidepressant (AD) treatment for major depressive disorder (MDD) remains 50-75%[1].
- Most frequently employed management option for treatment resistant depression and also recommended in treatment guidelines [2,3] is the co-treatment with a second antidepressant [4].
- However, evidence for the efficacy advantages of AD co-treatment is slim [5], and concerns about an increased adverse effect (AE) burden have been raised.
- In order to allow for a comprehensive risk-benefit analysis of AD+AD co-treatment, detailed knowledge about its short-term and long-term tolerability in patients with MDD is needed.
- Therefore, we conducted a systematic review and meta-analysis of the frequency and severity of AEs in patients with MDD co-treatment compared with AD monotherapy, hypothesizing that the risk of AEs would be significantly greater with AD+AD co-treatment.

METHOD

Systematic PubMed/Medline/PsycInfo/Embase search from database inception through 06/01/2015

Inclusion criteria

- Randomized controlled trials, including ≥20 patients with MDD
- Studies reporting the frequency or severity of AEs in patients who were randomized to either AD+AD co-treatment or to AD monotherapy, of the same AD that was also a part of the AD+AD combination

Outcomes

Co-Primary:
- Intolerability-related discontinuation
- Proportion of patients with at least one AE

Secondary:
- Incidence of any specific AE
- Severity of any specific adverse event

Analysis

Random-effects meta-analysis of outcomes for which ≥2 studies contributed data, calculating the Risk Ratio (RR) with its 95% confidence interval (CI) for categorical outcomes and the Standardized Mean Difference (SMD) with its CI for continuous outcomes.

FLOW DIAGRAM FOR ARTICLE SELECTION

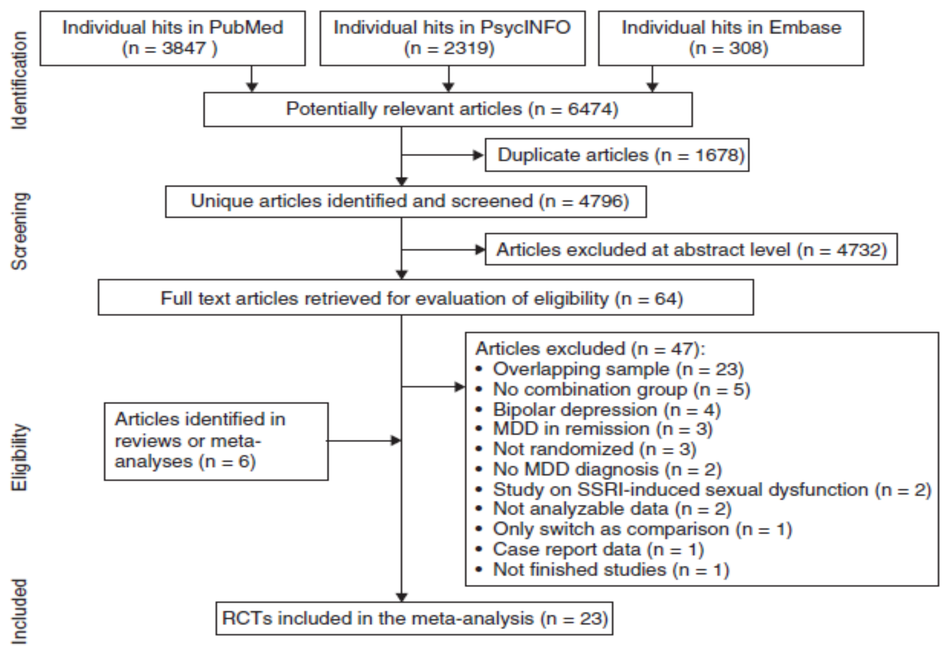

Figure 1. Flow chart for the systematic literature search.

RESULTS OF OUTCOME MEASURES

Outcomes	All Studies			Augmentation Studies			Combination Studies		
	N (n)	RR/SMD	P-Value	N (n)	RR/SMD	P-Value	N (n)	RR/SMD	P-Value
Discontinuation due to AE	18 (1270)	1.368	0.149	3 (323)	1.737	0.471	15 (947)	1.434	0.142
At least 1 AE	9 (1029)	1.185	0.142	3 (589)	1.498	<0.001	6 (440)	0.982	0.824
Tremor	4 (576)	1.552	0.044	1 (293)	1.327	0.656	3 (283)	1.585	0.047
Sweating	7 (928)	1.951	0.017	2 (519)	2.530	0.326	5 (409)	2.016	0.045
>7%Weight gain	3 (401)	3.1148	0.009	2 (363)	3.807	0.010	1 (38)	2.000	0.388
Body weight Change (SMD)	2 (346)	1.033	0.008	1 (293)	0.692	<0.001	1 (53)	1.476	<0.001
Body weight change (WMD)	2 (346)	2.170	0.004	1 (293)	1.500	<0.001	1 (53)	3.000	<0.001

Other side effects assessed with non-significant results: Dry mouth, Blurred vision, Sedation, Fatigue, Asthenia, Insomnia, Fainting/Dizziness, Tachycardia, Confusion, Mania, Inner restlessness, Headache, Constipation, Diarrhea, Nausea, Abdominal discomfort, Decreased appetite, Sexual dysfunction, Paresthesia

Note: AE=Adverse effects; N=Number of studies; n= number of subjects; NaSSA=Noradrenergic and Specific Serotonin Antagonist; RR: Risk Ratio; SSRI=Selective Serotonin Reuptake Inhibitor, SMD=Standardized mean difference; TCA=Tricyclic Antidepressants; WMD=Weighted mean difference

SUMMARY OF RESULTS

Total Sample: 23 meta-analyzed studies
(n=2435, duration=6.6 weeks)

1. Intolerability-related discontinuation

- AD+AD co-treatment and AD monotherapy were similar regarding intolerability-related discontinuatio

2. Frequency of at least one Adverse Event (AE)

- Overall, AD+AD co-treatment and AD monotherapy were similar regarding frequency of patients with ≥ 1 AE. However, Augmentation studies only evidenced increased rate of ≥ 1 AE

3. Specific Adverse Events

- AD+AD co-treatment was associated with significantly greater burden regarding 4/25 AEs (Tremo, Sweating, Weight gain, Clinically significant weight gain (Table 1)
- No more central nervous system, gastrointestinal, sexual or alertness-related AEs.

CONCLUSION

- AD+AD co-treatment strategies do not appear to be associated with significantly greater intolerability-related discontinuation and increased incidence of ≥1AE.
- AD+AD co-treatment strategies were associated with a significantly greater incidence or severity of 4 of 25 specific reported AEs (tremor, sweating, weight gain and clinically significant weight gain) than AD monotherapy strategies,
- Adverse events were more common with SSRI+ NaSSA (weight gain and sedation) and SSRI + TCA (dry mouth and sedation)
- Frequencies and severity of global and specific AEs are insufficiently and incompletely assessed or reported.
- Clearly, more data on side-effect burden of AD+AD co-treatment are needed and such data need to be complemented by high quality and more definitive information about the efficacy .

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