# 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 25-50%[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
- Reporting on 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*

We conducted a 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.

## Result

**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 discontinuation (N=18, n=1270, RR=1.38, 95%CI=0.89-1.10, p=0.80)

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

AD+AD co-treatment and AD monotherapy were similar regarding frequency of patients with ≥ 1 AE (N=9, n=1029, RR=1.19, 95% CI=0.95-1.49, p=0.14)

*3. Specific Adverse Events*

- AD+AD co-treatment was associated with significantly greater burden regarding 4/25 AEs (Tremor: RR=1.55, 95% CI=1.01-2.38, p=0.044;
- Sweating: RR=1.95, 95% CI=1.13-3.38, p=0.017; ≥7%Weight gain: RR=3.15, 95% CI=1.34-7.41, p=0.009; Weight gain: SMD=1.03, 95%CI=0.27-1.79, p=0.008)
- No more central nervous system, gastrointestinal, sexual or alertness-related AEs.

## Table depicting the results of outcomes measures

| Outcome | All studies | | | | | | Augmentation-studies | | | | | | Combination treatment-studies | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Outcome** | **N** | **n** | **Risk ratio/ SMD** | **95% CI** | **p-Value** | **p-Value heterogeneity** | **N** | **n** | **Risk ratio/ SMD** | **95% CI** | **p-Value** | **p-Value heterogeneity** | **N** | **N** | **Risk ratio/ SMD** | **95% CI** | **p-Value** | **p-Value heterogeneity** |
| *Co-primary outcomes* | | | | | | | | | | | | | | | | | | |
| Discontinuation due to AE | 18 | 1270 | 1.368 | 0.894, 2.096 | 0.149 | 0.797 | 3 | 323 | 1.737 | 0.386, 7.807 | 0.471 | 0.220 | 15 | 947 | 1.434 | 0.887, 2.319 | 0.142 | 0.833 |
| At least one AE | 9 | 1029 | 1.185 | 0.945, 1.486 | 0.142 | < 0.001 | 3 | 589 | AD mono ↑ 1.498‡ | 1.299, 1.726‡ | < 0.001§ | 0.406 | 6 | 440 | 0.982 | 0.840, 1.149 | 0.824 | 0.140 |
| *Movement disorder* | | | | | | | | | | | | | | | | | | |
| Tremor | 4 | 576 | AD mono ↑ 1.552‡ | 1.012, 2.380‡ | 0.044§ | 0.811 | 1 | 293 | 1.327 | 0.383, 4.592 | 0.656 | – | 3 | 283 | AD mono ↑ 1.585‡ | 1.006, 2.499‡ | 0.047§ | 0.640 |
| Anticholinergic AE | | | | | | | | | | | | | | | | | | |
| Dry mouth/ reduced salivation | 8 | 839 | 1.516 | 0.910, 2.526 | 0.110 | 0.002§ | 3 | 430 | AD mono ↑ 2.082‡ | 1.234, 3.513‡ | 0.006§ | 0.403 | 5 | 409 | 1.289 | 0.674, 2.465 | 0.443 | 0.002§ |
| Blurred vision | 2 | 65 | 2.265 | 0.556, 9.230 | 0.254 | 0.730 | 1 | 27 | 3.692 | 0.164, 83.268 | 0.411 | – | 1 | 38 | 2.000 | 0.415, 9.650 | 0.388 | – |
| *Arousal-related AE* | | | | | | | | | | | | | | | | | | |
| Sedation | 5 | 636 | 1.655 | 0.858, 3.194 | 0.133 | 0.023§ | 1 | 293 | AD mono ↑ 3.198‡ | 2.134, 4.792‡ | < 0.001§ | – | 4 | 343 | 1.149 | 0.700, 1.888 | 0.583 | 0.675 |
| Fatigue/tiredness/drowsiness | 5 | 420 | 1.227 | 0.749, 2.010 | 0.418 | 0.445 | 2 | 137 | 2.018 | 0.511, 7.975 | 0.317 | 0.251 | 3 | 283 | 1.052 | 0.578, 1.915 | 0.867 | 0.431 |
| Asthenia/lack of energy | 2 | 108 | 0.739 | 0.254, 2.150 | 0.579 | 0.325 | 1 | 70 | 0.297 | 0.035, 2.524 | 0.266 | – | 1 | 38 | 1.000 | 0.292, 3.426 | 1.000 | – |
| Insomnia | 6 | 702 | 0.855 | 0.566, 1.291 | 0.456 | 0.202 | 1 | 293 | 1.279 | 0.574, 2.851 | 0.547 | – | 5 | 409 | 0.778 | 0.481, 1.257 | 0.305 | 0.180 |
| *Cardiovascular AE* | | | | | | | | | | | | | | | | | | |
| Fainting/ Dizziness | 8 | 839 | 1.063 | 0.754, 1.498 | 0.729 | 0.998 | 3 | 430 | 1.074 | 0.610, 1.892 | 0.804 | 0.791 | 5 | 409 | 1.056 | 0.685, 1.627 | 0.805 | 0.990 |
| Tachycardia | 3 | 164 | 0.836 | 0.192, 3.640 | 0.811 | 0.215 | 0 | 0 | – | – | – | – | 3 | 164 | 0.836 | 0.192, 3.640 | 0.811 | 0.215 |
| *CNS AE* | | | | | | | | | | | | | | | | | | |
| Confusion | 3 | 283 | 1.470 | 0.754, 2.867 | 0.258 | 0.419 | 0 | 0 | – | – | – | – | 3 | 283 | 1.470 | 0.754, 2.867 | 0.258 | 0.419 |
| Mania | 4 | 393 | 0.995 | 0.455, 2.176 | 0.990 | 0.549 | 0 | 0 | – | – | – | – | 4 | 393 | 0.995 | 0.455, 2.176 | 0.990 | 0.549 |
| Tension/inner restlessness | 3 | 419 | 0.684 | 0.305, 1.536 | 0.358 | 0.932 | 1 | 293 | 0.569 | 0.120, 2.686 | 0.476 | – | 2 | 126 | 0.733 | 0.284, 1.891 | 0.521 | 0.799 |
| Headache | 7 | 772 | 1.022 | 0.747, 1.400 | 0.890 | 0.797 | 2 | 363 | 0.707 | 0.142, 3.514 | 0.671 | 0.227 | 5 | 409 | 1.038 | 0.746, 1.445 | 0.823 | 0.819 |
| *Gastrointestinal AE* | | | | | | | | | | | | | | | | | | |
| Constipation | 3 | 164 | 0.951 | 0.190, 4.769 | 0.952 | 0.025§ | 1 | 38 | 1.000 | 0.474, 2.108 | 1.000 | – | 2 | 126 | 1.430 | 0.025, 81.597 | 0.862 | 0.012 |
| Diarrhea | 2 | 331 | 0.448 | 0.188, 1.065 | 0.069 | 0.771 | 1 | 293 | 0.474 | 0.184, 1.218 | 0.121 | – | 1 | 38 | 0.333 | 0.038, 2.925 | 0.322 | – |
| Nausea | 8 | 1007 | 0.918 | 0.683, 1.234 | 0.570 | 0.723 | 3 | 589 | 1.411 | 0.643, 3.097 | 0.390 | 0.312 | 5 | 418 | 0.840 | 0.604, 1.168 | 0.299 | 0.949 |
| Abdominal pain/ GI distress | 2 | 137 | 0.890 | 0.557, 1.421 | 0.625 | 0.377 | 2 | 137 | 0.890 | 0.557, 1.421 | 0.625 | 0.377 | 0 | 0 | – | – | – | – |
| Decreased appetite | 3 | 283 | 0.827 | 0.521, 1.313 | 0.422 | 0.842 | 0 | 0 | – | – | – | – | 3 | 283 | 0.827 | 0.521, 1.313 | 0.422 | 0.842 |
| *Weight change AE* | | | | | | | | | | | | | | | | | | |
| Weight gain ≥ 7% or reported as side effect | 3 | 401 | AD monosu-perior 3.148‡ | 1.338, 7.405‡ | 0.009§ | 0.511 | 2 | 363 | AD monosu-perior 3.807‡ | 1.374, 10.548‡ | 0.010§ | 0.348 | 1 | 38 | 2.000 | 0.415, 9.650 | 0.388 | – |
| Body weight change (SMD)* | 2 | 346 | *AD monosu-perior* 1.033‡ | *0.271, 1.794‡* | *0.008§* | *0.019§* | 1 | 293 | *AD monosu-perior 0.692‡* | *0.443, 0.941‡* | *< 0.001§* | – | 1 | 53 | *AD monosu-perior 1.476‡* | *0.868, 2.084‡* | *< 0.001§* | – |
| Body weight change (WMD: kg)* | 2 | 346 | *AD monosu-perior 2.170‡* | *0.708, 3.631‡* | *0.004§* | *0.016§* | 1 | 293 | *AD monosu-perior 1.500‡* | *0.974, 2.026‡* | *< 0.001§* | – | 1 | 53 | *AD monosu-perior 3.000‡* | *1.904, 4.096‡* | *< 0.001§* | – |
| *Endocrine AE* | | | | | | | | | | | | | | | | | | |
| Sexual dysfunction (any) | 5 | 569 | 1.403 | 0.861, 2.287 | 0.174 | 0.378 | 1 | 226 | 5.179 | 0.251, 106.673 | 0.287 | – | 4 | 343 | 1.346 | 0.793, 2.284 | 0.271 | 0.323 |
| *Other AEs* | | | | | | | | | | | | | | | | | | |
| Paresthesia | 2 | 264 | 1.818 | 0.553, 5.973 | 0.325 | 0.720 | 1 | 226 | 3.107 | 0.128, 75.472 | 0.486 | – | 1 | 38 | 1.667 | 0.462, 6.008 | 0.435 | – |
| Sweating/ Perspiration | 7 | 928 | AD monosu-perior 1.951‡ | 1.127, 3.376‡ | 0.017§ | 0.057 | 2 | 519 | 2.530 | 0.398, 16.092 | 0.326 | 0.078§ | 5 | 409 | AD monosu-perior 2.016‡ | 1.017, 3.996‡ | 0.045§ | 0.059 |

## Flow diagram for literature search

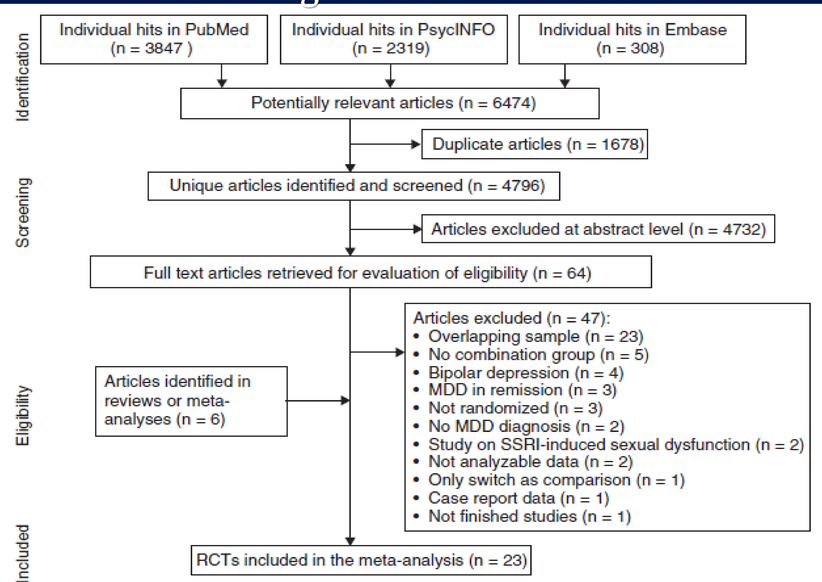


**Figure 1. Flow chart for the systematic literature search.**

## 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 than AD monotherapy strategies.
- Specific AEs more common during antidepressant (AD) + AD co-treatment included tremor, sweating, weight gain and clinically significant weight gain.
- Frequencies and severity of global and specific AEs are insufficiently and incompletely assessed or reported in the available randomized controlled studies.
- 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 of this frequently employed clinical strategy.

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