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# Individual Differences in Response to Antidepressants
## A Meta-analysis of Placebo-Controlled Randomized Clinical Trials

Marta M. Maslej, PhD; Toshiaki A. Furukawa, MD, PhD; Andrea Cipriani, MD, PhD; Paul W. Andrews, PhD, JD; Benoit H. Mulsant, MD, MS, FRCPC

**IMPORTANCE** Antidepressants are commonly used worldwide to treat major depressive disorder. Symptomatic response to antidepressants can vary depending on differences between individuals; however, this variability may reflect nonspecific or random factors.

**OBJECTIVES** To investigate the assumption of systematic variability in symptomatic response to antidepressants and to assess whether this variability is associated with severity of major depressive disorder, antidepressant class, or year of study publication.

**DATA SOURCES** Data used were from a recent network meta-analysis of acute treatment with licensed antidepressants in adults with major depressive disorder. The following databases were searched from inception to January 8, 2016: the Cochrane Central Register of Controlled Trials, CINAHL, Embase, LILACS database, MEDLINE, MEDLINE In-Process, and PsycINFO. Additional sources were international trial registries, drug approval agency websites, and key scientific journals.

**STUDY SELECTION** Analysis was restricted to double-blind, randomized placebo-controlled trials with available data at the study's end point.

**DATA EXTRACTION AND SYNTHESIS** Baseline and end point means, SDs, number of participants in each group, antidepressant class, and publication year were extracted. The data were analyzed between August 14 and November 18, 2019.

**MAIN OUTCOMES AND MEASURES** With the use of validated methods, coefficients of variation were derived for antidepressants and placebo, and their ratios were calculated to compare outcome variability between antidepressant and placebo. Ratios were entered into a random-effects model, with the expectation that response to antidepressants would be more variable than response to placebo. Analysis was repeated after stratifying by baseline severity of depression, antidepressant class (selective serotonin reuptake inhibitors: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and vilazodone; serotonin and norepinephrine reuptake inhibitors: desvenlafaxine and venlafaxine; norepinephrine-dopamine reuptake inhibitor: bupropion; noradrenergic agents: amitriptyline and reboxetine; and other antidepressants: agomelatine, mirtazapine, and trazodone), and publication year.

**RESULTS** In the 87 eligible randomized placebo-controlled trials (17 540 unique participants), there was significantly more variability in response to antidepressants than to placebo (coefficients of variation ratio, 1.14; 95% CI, 1.11-1.17; $P < .001$). Baseline severity of depression did not moderate variability in response to antidepressants. Variability in response to selective serotonin reuptake inhibitors was lower than variability in response to noradrenergic agents (coefficients of variation ratio, 0.88; 95% CI, 0.80-0.97; $P = .01$), as was the variability in response to other antidepressants compared with noradrenergic agents (coefficients of variation ratio, 0.87; 95% CI, 0.79-0.97; $P = .001$). Variability also tended to be lower in studies that were published more recently, with coefficients of variation changing by a value of 0.005 (95% CI, 0.002-0.008; $P = .003$) for every year a study is more recent.

**CONCLUSIONS AND RELEVANCE** Individual differences may be systematically associated with responses to antidepressants in major depressive disorder beyond placebo effects or statistical factors. This study provides empirical support for identifying moderators and personalizing antidepressant treatment.

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Editorial
Supplemental content

**Author Affiliations:** Author affiliations are listed at the end of this article.

**Corresponding Author:** Benoit H. Mulsant, MD, MS, FRCPC, Centre for Addiction and Mental Health, University of Toronto, 250 College St, Ste 835, Toronto, ON M5T 1R8, Canada (benoit.mulsant@utoronto.ca).

Major depressive disorder (MDD) is a common and heterogeneous mental health condition characterized by emotional, cognitive, somatic, and behavioral symptoms.[1] Antidepressants (ADs) are the first-line intervention for depression,[2] but their efficacy is variable. Many individuals experience remission of depression with treatment, but more than 50% of patients improve very little or their depression worsens.[3] Such substantial variation observed in response to psychiatric medications has prompted efforts to identify moderators of treatment response and to personalize treatments to match ADs with the unique characteristics of individual patients.[4-6] However, the variability in the efficacy of psychiatric medications is often deduced from randomized clinical trials (RCTs), which estimate average treatment effects.[5,6] Outcomes in RCTs may vary systematically based on individual differences as well as random factors or other factors, such as placebo effects, regression to the mean, or measurement error.[6] Detecting treatment by individual interactions requires more complex study designs.[7]

In the case of antipsychotics, a recent study suggests that random factors account for the observed variability in response to these medications: Winkelbeiner and colleagues[6] performed a meta-analysis of RCTs comparing the variability in outcomes for participants assigned to receive an antipsychotic or a placebo. They hypothesized that if responses to antipsychotics included systematic individual differences in addition to other factors (eg, placebo effects or statistical factors), those responses should be more variable than responses to placebo. They found that placebo produced slightly more variable outcomes, calling into question the widely held assumption that variability in response to antipsychotics may be due to individual differences.[6]

As with antipsychotics, there is a widely held assumption that individual differences underlie the variability in the association of ADs with depressive symptoms (ie, response).[8-11] Data from RCTs show that depressed individuals assigned to receive the same AD at the same dose and for the same period can experience very different outcomes.[5] The source of this variability is widely believed to result from individual differences. However, to our knowledge, efforts to identify factors associated with response to specific ADs or to AD classes have generally been unsuccessful.[4,5,12-14] Nevertheless, depression appears to be a more heterogeneous condition than schizophrenia, and the unexplained source of its heterogeneity may account for some of the observed variability in AD treatment outcomes.[15,16]

Although depressive symptoms have been organized into various clusters or profiles, there does not appear to be a profile experienced by a substantial proportion of individuals with depression.[15-17] Based on these findings, some have suggested that depression is a variety of conditions differing in cause, symptom presentation, and biological predisposition.[16] This heterogeneity may produce differences in treatment response, with patients who have different symptom clusters or condition types responding to different ADs. If some ADs are more effective at treating emotional symptoms of depression, whereas others are more effective at treating its somatic symptoms,[15] such differences would be consistent with the assumption that individuals vary systematically (rather than randomly) in their response to ADs. Given that the ability to personalize AD treatments for depression rests on the validity of this assumption, it is important to evaluate it more rigorously.

### Key Points

**Question** Is there evidence that response to antidepressants varies systematically based on individual differences?

**Findings** In a meta-analysis of 87 randomized clinical trials (17 540 unique participants) on the use of antidepressants in individuals with major depression, there was 14% more variability in response to antidepressants than to placebo. Baseline severity of depression did not moderate this variability, but variability in response to noradrenergic agents was higher than that of selective serotonin reuptake inhibitors and antidepressants classified as other; variability also tended to be lower in studies published more recently.

**Meaning** Response to antidepressants may include individual differences, which are associated with variability beyond nonspecific random or statistical factors, with some evidence that antidepressant class and publication year are associated with variability.

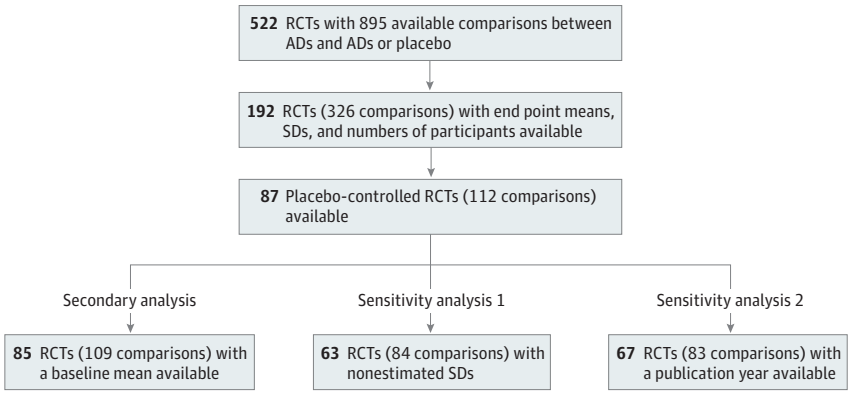
The primary aim of our analysis was to examine whether there is systematic variability in symptomatic response to ADs among patients with MDD. By comparing variability in outcomes for participants assigned to receive ADs or placebo, we assessed whether the observed variability in response to ADs is due to systematic, nonrandom factors. We hypothesized that variability in response to ADs would include an individual by treatment interaction and differ from the variability in response to placebo.

We also examined whether baseline severity of depression, AD class, or the year in which studies were published is associated with variability in response to ADs. We hypothesized that responses in studies involving participants whose symptoms were initially more severe would be more variable, since the effects of ADs appear to be more pronounced in individuals with severe depression.[18,19] We also expected that variability might differ based on the way that different AD classes interact with different neurotransmitter systems. Specifically, we hypothesized that ADs affecting multiple neurotransmitter systems would produce more variable outcomes than would ADs with more selective effects.

## Methods

We used publicly available data from a published network meta-analysis of 522 RCTs evaluating the effects of ADs on MDD.[20] The methods and descriptive statistics for this meta-analysis are published elsewhere.[20,21] Briefly, selected databases (the Cochrane Central Register of Controlled Trials, CINAHL, Embase, LILACS database, MEDLINE, MEDLINE In-Process, and PsycINFO) were searched from their inception to January 8, 2016, using terms that included references to depression in combination with a list of ADs. Additional sources were international trial registries, drug approval agency websites, and key scientific journals. Of the included RCTs, 252 of 522 (48%) were conducted in North America, 140 of 522

Figure 1. Study Selection Process




AD indicates antidepressant; RCT, randomized clinical trial.

(27%) in Europe, and 37 of 522 (7%) in Asia, with the remaining studies being cross-continental or from other regions. There was a total of 87 052 participants allocated to an AD and 29 425 allocated to a placebo. Participants' mean (SD) age was 44 (9) years, and 63% were women. Most participants had moderate or severe depression. The included studies assessed depressive symptoms using one of several versions of the Hamilton Rating Scale for Depression (HAMD-17,[22] HAMD-21,[22] HAMD-24,[23] HAMD-29,[24] and HAMD-31[25]), the Montgomery Asberg Depression Rating Scale,[26] or the Inventory of Depressive Symptomatology.[27] End point scores were extracted as close to 8 weeks after the start of AD treatment or placebo as possible, with the median duration being 8 weeks (interquartile range, 6-8 weeks).[20] The data were analyzed between August 14 and November 18, 2019.

## Eligibility Criteria

Our analysis included only placebo-controlled RCTs with available data at end point (means, SDs, and number of participants assessed in each group). **Figure 1** depicts our selection process and the resulting number of included RCTs. From the publicly available data[20] corresponding to the eligible RCTs, we extracted baseline and end point means, SDs, number of participants in each group, AD class, and, when available, the year of RCT publication.

## Statistical Analysis

### Primary Analysis

Following statistical methods used in the previous work focused on antipsychotics,[6,28,29] we calculated coefficients of variation for ADs and for placebo by dividing the SD by the mean depression score at end point. Then, we generated natural logs of the ratios between the coefficients of variation (CVRs) for each comparison between an AD and placebo in the eligible RCTs using the following formula[29]:

$$\ln CVR = \ln\left(\frac{CV_{AD}}{CV_{PB}}\right) + \frac{1}{2(n_{AD}-1)} - \frac{1}{2(n_{PB}-1)},$$

where $n_{AD}$ refers to the number of participants in the AD group and $n_{PB}$ refers to the number of participants in the placebo group.

We used the following formula to derive sampling variances[29]:

$$s^2_{lnCVR} = \frac{s^2_{PB}}{n_{PB}\bar{x}^2_{PB}} + \frac{1}{2(n_{PB}-1)} - 2\rho_{ln\,\bar{x}_{PD},ln\,s_{PB}}\sqrt{\frac{s^2_{PB}}{n_{PD}\bar{x}^2_{PB}}}\frac{1}{2(n_{PB}-1)} + \frac{s^2_{AD}}{n_{AD}\bar{x}^2_{AD}} + \frac{1}{2(n_{AD}-1)} - 2\rho_{ln\,\bar{x}_{AD},ln\,s_{AD}}\sqrt{\frac{s^2_{AD}}{n_{AD}\bar{x}^2_{AD}}}\frac{1}{2(n_{AD}-1)},$$

where $s$ refers to SD, $\bar{x}$ refers to mean, and $\rho_{ln\,\bar{x},ln\,s}$ refers to the correlation between the mean and SD in each group on the log scale.[29] We weighted each natural log CVR with the inverse of its sampling variance and entered it into a random-effects model. We back-transformed the results from the log scale, such that a ratio higher than 1 was consistent with our hypothesis, indicating higher variability in AD groups than placebo groups. Conversely, a ratio lower than 1 indicated less variability in the AD groups compared with placebo groups.[6]

### Secondary Analyses

We repeated our primary analyses stratified by baseline severity of depression and AD class. Because baseline means were measured using different depression scales, we rescaled means to have the same upper and lower limits (ie, 0 and 100) based on their existing ranges using the scales package in R, version 3.5.1 (R Project for Statistical Computing). For each RCT, we averaged the standardized baseline means across conditions. We categorized baseline symptom severity in each RCT as minimal, midrange, or severe by using lower and upper mean interquartile ranges as our classification criteria. We entered the CVRs from each eligible RCT with a baseline mean available (Figure 1) into a mixed-effects model, specifying the baseline severity category as a moderator. We examined CVRs separately for each category, and we tested the significance of the moderator with $Q_M$. To compare variability between categories, we examined CVRs estimated by the mixed-effects model to reflect a comparison between the midrange severity category (the reference group) and the other 2 categories (ie, minimal and severe). In these comparisons, CVRs less than 1 indicated less variability in that category compared with the reference group.

For each available comparison from the eligible RCTs, we categorized the ADs into one of the following 5 classes based on their main putative mechanisms of action: selective

serotonin reuptake inhibitors (SSRIs) (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and vilazodone); serotonin and norepinephrine reuptake inhibitors (SNRIs) (desvenlafaxine and venlafaxine); norepinephrine-dopamine reuptake inhibitors (NDRIs) (bupropion); noradrenergic agents (NAs) (amitriptyline and reboxetine); and other ADs (agomelatine, mirtazapine, and trazodone). We entered CVRs into a second mixed-effects model after specifying AD class as a moderator, and we examined CVRs separately for each class. We tested the significance of the moderator with an omnibus test of coefficients ($Q_M$) and examined CVRs reflecting comparisons between NAs (the reference group) and the remaining AD classes.

### Sensitivity Analyses

First, we repeated our primary analysis using only RCTs in which SDs were not imputed from other studies,[20,21] to determine whether these imputations were associated with our primary finding. In a second sensitivity analysis, we investigated whether the year in which RCTs were published was associated with our findings. Using only RCTs with a publication year available (Figure 1), we repeated our primary and secondary analyses with publication year as a moderator. For the primary analysis, we generated a mixed-effects model specifying year as a continuous moderator, and we tested its significance with $Q_M$. To illustrate how CVRs change as a function of publication year, we generated the 5 CVRs predicted by this model for the years 1975, 1985, 1995, 2005, and 2015. For the secondary analyses, we added publication year to the existing categorical moderators (ie, depression severity and AD class) in mixed-effects models. We also generated predicted CVRs for the years 1975, 1985, 1995, 2005, and 2015 for each comparison of moderator categories.

All analyses were completed in R, version 3.5.1, using the Metafor package and using the *escalc* function to calculate CVRs and their sampling variances, the *rma* function for random-effects modeling, and the *predict* function for predicting CVRs stratified by publication year.[30] The significance threshold was .05, and significance testing was 2-sided. To ensure reproducibility, our data[31] and code[32] are freely available online.

## Results

### Primary Analysis

A total of 87 RCTs comprising 17 540 unique participants met our inclusion criteria. To measure outcomes at end point, 41 RCTs (47%) used the HAMD-17 and 33 (38%) used the HAMD-21. Because some RCTs compared placebo with more than 1 AD (ie, multiarm trials), 112 comparisons were available (Figure 1). There was 14% more variability in responses to ADs compared with placebo (CVR = 1.14; 95% CI, 1.11-1.17; $P < .001$). **Figure 2** and **Figure 3** present a forest plot of CVRs and 95% CIs.[20,33-103]

### Secondary Analyses

#### Depression Severity

There were 85 placebo-controlled RCTs with both baseline and end point means available, corresponding to 109 comparisons (Figure 1). Rescaled baseline mean depressive scores (averaged across study conditions) ranged between 25.37 and 81.85 (mean [SD], 44.09 [7.97]; interquartile range, 39.85-48.70). Based on the interquartile range, means less than 39.85 were categorized as indicating minimal depression, means from 39.85 to 48.70 were categorized as midrange, and means larger than 48.70 were categorized as severe. Using these criteria, participants from 22 studies were on average minimally depressed at baseline, participants from 22 studies were on average severely depressed at baseline, and participants from 41 studies were in the midrange at baseline (the number of observations available for each category is provided in **Table 1**).

Responses to ADs were more variable than responses to placebo in each of the 3 severity subgroups (Table 1). Baseline severity of depression did not moderate variability ($Q_M = 0.30$; $df = 2$; $P = .86$). Variability in responses between ADs and placebo in individuals whose symptoms were in the midrange did not differ from those whose symptoms were minimal or severe (Table 1).

#### AD Class

Responses to all AD classes were more variable than responses to placebo (Table 1). Antidepressant class did not moderate the variability of responses to a significant degree ($Q_M = 9.08$; $df = 4$; $P = .06$). Variability in responses to NAs (ie, the reference group) did not differ from responses to NDRIs or SNRIs (Table 1). However, variability in responses to SSRIs was lower than variability in responses to NAs (CVR = 0.88; 95% CI, 0.80-0.97; $P = .01$), and variability in responses to other ADs was lower than variability in responses to NAs (CVR = 0.87; 95% CI, 0.79-0.97; $P = .001$) (Table 1). Findings from this secondary analysis suggest that ADs affecting synaptic norepinephrine (ie, NAs, NDRIs, and SNRIs) produce a similar variability in symptomatic response, higher than the variability in response to ADs that affect only synaptic serotonin (ie, SSRIs). To test this assertion, we conducted an additional post hoc analysis. We repeated our analysis grouping ADs with any noradrenergic reuptake–inhibiting properties (ie, NAs, NDRIs, and SNRIs; 37 comparisons) in one class. In this analysis, AD class moderated the variability of responses significantly ($Q_M = 6.94$; $df = 2$; $P = .03$). Variability in responses to SSRIs was lower than variability in responses to ADs with noradrenergic reuptake–inhibiting properties (CVR, 0.93; 95% CI, 0.87-0.99; $P = .02$). Variability in responses to other ADs was also lower than variability in responses to ADs with noradrenergic reuptake–inhibiting properties (CVR, 0.92; 95% CI, 0.86-0.99; $P = .02$).

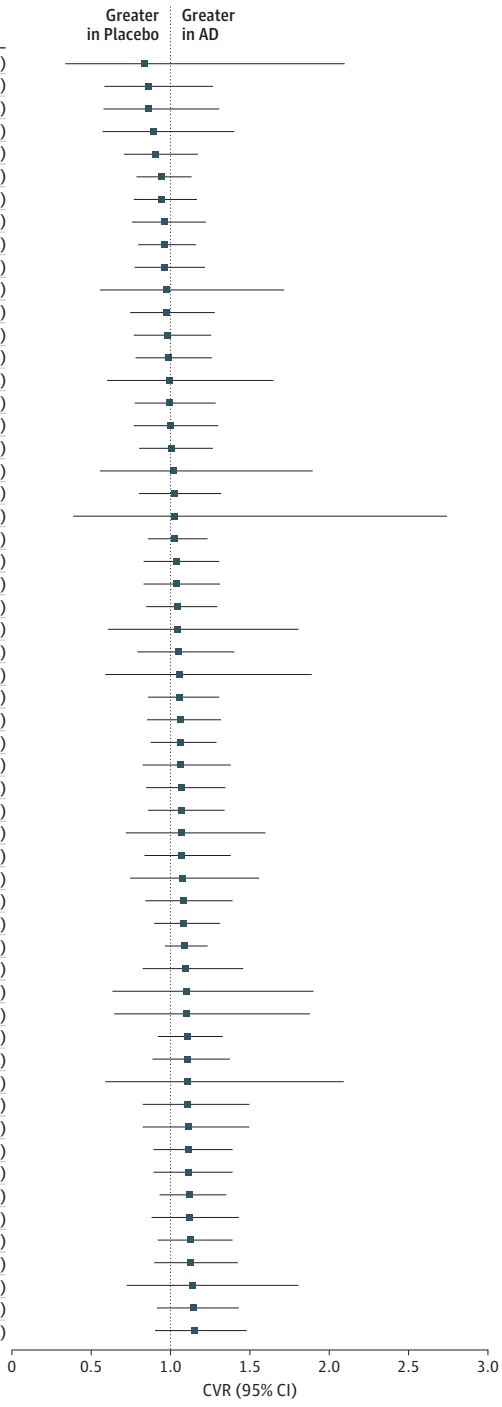
#### Sensitivity Analyses

**Analysis 1 |** We assessed whether imputation of some SDs was associated with our primary finding of more variability in responses to ADs than to placebo. When we restricted our analysis to the 63 RCTs[20,33,34,36-47,49,50,52-72,74-76,79,80,82,86,87,92,93,95,97,99,102] (corresponding to 84 comparisons) for which SDs were not estimated, our findings did not qualitatively differ from those derived from all outcomes (CVR, 1.13; 95% CI, 1.10-1.16; $P < .001$).

**Analysis 2 |** We examined whether the year of RCT publication was associated with our primary and secondary findings. The 67 RCTs[20,67-82,84-100,102,103] with a publication year available,

Figure 2. Forest Plot Depicting Coefficient of Variation Ratios (CVRs), 95% CIs, and the Summary Statistics for All Available Comparisons Between Antidepressant and Placebo

| Source | No. of Participants | CVR (95% CI) |
|---|---|---|
| MIR84064,[20] NA | 30 | 0.84 (0.33-2.10) |
| Barber et al,[33] 2011 | 105 | 0.86 (0.58-1.26) |
| Wellbutrin 25,[20] NA | 73 | 0.87 (0.58-1.31) |
| Study 032a,[34] NA | 47 | 0.90 (0.57-1.40) |
| Schatzberg et al,[35] 2006 | 195 | 0.91 (0.70-1.17) |
| CAGO178A2303,[36] NA | 320 | 0.94 (0.78-1.13) |
| CL3-20098-024,[37] NA | 304 | 0.94 (0.77-1.17) |
| PZ/111,[38] NA | 213 | 0.96 (0.76-1.22) |
| Zajecka et al,[39] 2010 | 323 | 0.96 (0.80-1.16) |
| FDA248,[40] NA | 260 | 0.97 (0.77-1.21) |
| WELL029,[20] NA | 39 | 0.98 (0.56-1.72) |
| 003-048,[20] NA | 238 | 0.98 (0.75-1.28) |
| Sheehan et al,[42] 2009 | 194 | 0.98 (0.77-1.25) |
| PZ/111,[38] NA | 211 | 0.99 (0.78-1.26) |
| Norton et al,[43] 1984 | 58 | 1.00 (0.60-1.65) |
| PZ/109,[38] NA | 207 | 1.00 (0.78-1.28) |
| Schatzberg et al,[35] 2006 | 189 | 1.00 (0.77-1.30) |
| FDA246,[40] NA | 248 | 1.01 (0.80-1.27) |
| Moreno et al,[44] 2005 | 46 | 1.03 (0.55-1.90) |
| Roffman et al,[45] 1982 | 188 | 1.03 (0.80-1.32) |
| MIR84062,[20] NA | 30 | 1.03 (0.39-2.74) |
| CL3-20098-024,[37] NA | 453 | 1.03 (0.86-1.24) |
| FDA246,[40] NA | 249 | 1.04 (0.83-1.31) |
| FDA248,[40] NA | 261 | 1.04 (0.83-1.31) |
| CL3-20098-022,[37] NA | 276 | 1.05 (0.85-1.29) |
| Fava et al,[46] 1998 | 73 | 1.05 (0.61-1.80) |
| Hirayasu,[47] 2011 | 196 | 1.05 (0.79-1.40) |
| Study 25,[48] NA | 38 | 1.06 (0.59-1.89) |
| CL3-20098-022,[37] NA | 280 | 1.06 (0.86-1.31) |
| CL3-20098-023,[49] NA | 278 | 1.06 (0.85-1.32) |
| AK1102365,[50] NA | 315 | 1.06 (0.87-1.29) |
| Nemeroff et al,[51] 2007 | 201 | 1.06 (0.82-1.38) |
| FDA246,[40] NA | 243 | 1.07 (0.84-1.35) |
| FDA247,[40] NA | 217 | 1.07 (0.86-1.34) |
| 845,[20] NA | 82 | 1.07 (0.72-1.60) |
| Rudolph et al,[52] 1999 | 200 | 1.07 (0.84-1.38) |
| Fava et al,[53] 2005 | 90 | 1.08 (0.75-1.56) |
| Study015,[34] NA | 221 | 1.08 (0.84-1.39) |
| Zajecka et al,[39] 2010 | 328 | 1.08 (0.90-1.31) |
| Schneider et al,[54] 2003 | 728 | 1.09 (0.97-1.23) |
| Hirayasu,[47] 2011 | 201 | 1.10 (0.82-1.46) |
| Fava et al,[46] 1998 | 74 | 1.10 (0.64-1.90) |
| Studie009,[34] NA | 47 | 1.10 (0.64-1.88) |
| Sheehan et al,[55] 2009 | 406 | 1.10 (0.92-1.33) |
| Loo et al,[56] 2002 | 280 | 1.11 (0.89-1.38) |
| PAR279MDUK,[57] NA | 29 | 1.11 (0.59-2.09) |
| 003-042,[20] NA | 135 | 1.11 (0.82-1.50) |
| 003-042,[20] NA | 135 | 1.11 (0.82-1.50) |
| Rickels et al,[58] 1985 | 245 | 1.11 (0.89-1.39) |
| Loo et al,[56] 2002 | 271 | 1.11 (0.89-1.39) |
| Stahl et al,[59] 2010 | 324 | 1.12 (0.93-1.35) |
| Lineberry et al,[60] 1990 | 216 | 1.12 (0.88-1.43) |
| Iwata et al,[61] 2013 | 467 | 1.13 (0.92-1.39) |
| Hirayasu,[62] 2011 | 243 | 1.13 (0.90-1.43) |
| Roth et al,[63] 1990 | 56 | 1.14 (0.72-1.81) |
| CL3-20098-023,[49] NA | 274 | 1.15 (0.92-1.43) |
| Khan et al,[64] 1998 | 182 | 1.15 (0.90-1.48) |



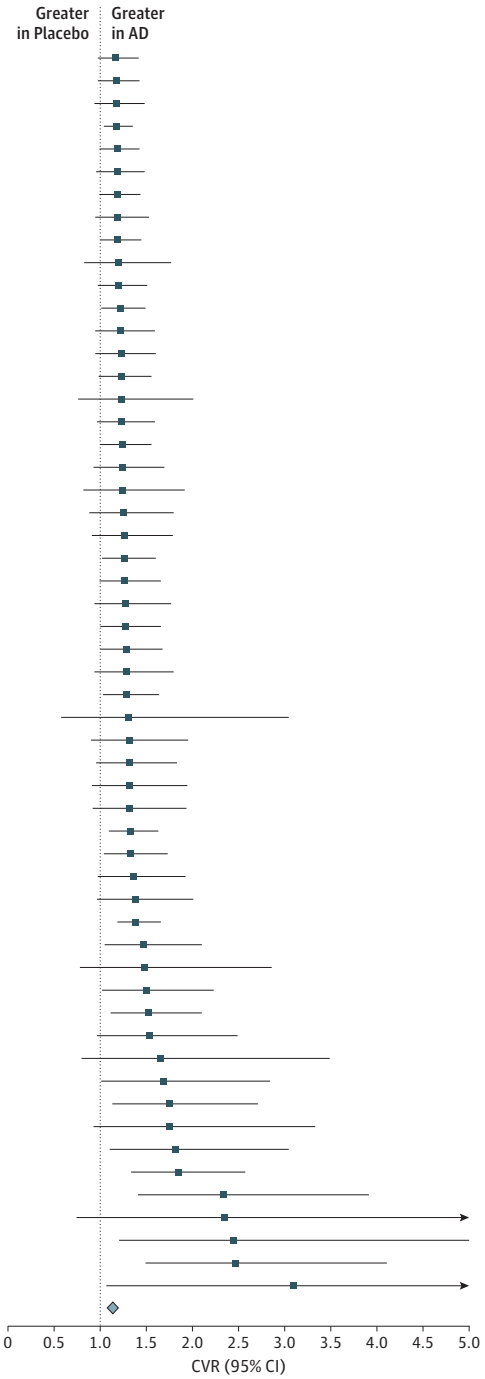

Multiple comparisons with the same placebo group were used from studies appearing more than once (ie, multi-arm trials). Numbers correspond to number of participants used for each comparison. Total number of unique participants is 17 540. There are no years available for unpublished sources. NA indicates year not applicable.

corresponding to 83 comparisons (Figure 1), were published between 1979 and 2014.

Publication year was a significant moderator of variability in responses to ADs compared with placebo ($Q_M$ = 9.03; *df* = 1; *P* = .003). For every year that an RCT was more recently published, the CVR decreased by 0.005 (95% CI, 0.002-0.008; *P* = .003). **Table 2** presents the CVRs predicted by the model for 1975, 1985, 1995, 2005, and 2015 and shows a decrease in variability as the years increased. When we added moderators from our secondary analyses (ie, baseline severity of depression and AD class), the association of publication year did not change (eResults in the Supplement). Variability tended to decrease for studies published more recently in each comparison of the 3 severity subgroups and

Figure 3. Forest Plot Depicting Coefficient of Variation Ratios (CVRs), 95% CIs, and the Summary Statistics for Available Comparisons Between Antidepressant and Placebo (Continued From Figure 2)

| Source | No. of Participants | CVR (95% CI) |
|---|---|---|
| Stahl et al,[59] 2010 | 321 | 1.16 (0.96-1.40) |
| Kennedy et al,[65] 2014 | 277 | 1.16 (0.96-1.41) |
| Hirayasu,[62] 2011 | 245 | 1.16 (0.92-1.47) |
| Tollefson et al,[66] 1995 | 655 | 1.17 (1.02-1.33) |
| Wade et al,[67] 2002 | 377 | 1.17 (0.97-1.41) |
| Gastpar et al,[68] 2006 | 257 | 1.17 (0.94-1.46) |
| CAGO178A2303,[36] NA | 321 | 1.17 (0.97-1.42) |
| Heun et al,[69] 2013 | 218 | 1.18 (0.92-1.51) |
| Zhang et al,[70] 2014 | 363 | 1.19 (0.99-1.43) |
| McGrath et al,[71] 2010 | 101 | 1.19 (0.81-1.75) |
| Olié et al,[72] 2007 | 235 | 1.19 (0.95-1.49) |
| Kennedy et al,[73] 2014 | 279 | 1.21 (0.99-1.47) |
| Rudolph et al,[52] 1999 | 192 | 1.21 (0.93-1.57) |
| Nemeroff et al,[51] 2007 | 197 | 1.21 (0.93-1.59) |
| Kennedy et al,[73] 2006 | 211 | 1.22 (0.96-1.54) |
| Lam et al,[74] 1995 | 68 | 1.22 (0.75-1.99) |
| Rapaport et al,[75] 2003 | 215 | 1.22 (0.94-1.58) |
| Silverstone et al,[76] 1999 | 237 | 1.23 (0.98-1.54) |
| 003-042,[20] NA | 135 | 1.23 (0.90-1.67) |
| Wellbutrin25,[20] NA | 75 | 1.23 (0.80-1.90) |
| Claghorn et al,[77] 1996 | 89 | 1.24 (0.87-1.78) |
| Rickels et al,[78] 1982 | 103 | 1.25 (0.89-1.77) |
| Silverstone et al,[76] 1999 | 240 | 1.26 (1.00-1.58) |
| Sheehan et al,[42] 2009 | 186 | 1.26 (0.97-1.64) |
| Feighner et al,[79] 1979 | 112 | 1.27 (0.92-1.75) |
| Khan et al,[64] 1998 | 176 | 1.27 (0.98-1.64) |
| Rapaport et al,[75] 2003 | 213 | 1.27 (0.98-1.65) |
| Feighner et al,[80] 1989 | 100 | 1.28 (0.91-1.78) |
| Hirayasu,[62] 2011 | 244 | 1.28 (1.01-1.62) |
| Tomarken et al,[81] 2004 | 18 | 1.29 (0.55-3.03) |
| Wellbutrin06,[20] NA | 75 | 1.30 (0.88-1.94) |
| Bjerkenstedt et al,[82] 2005 | 109 | 1.30 (0.94-1.81) |
| GSK14,[83] NA | 86 | 1.31 (0.89-1.92) |
| Mischoulon et al,[84] 2014 | 125 | 1.31 (0.90-1.92) |
| Amin et al,[85] 1984 | 311 | 1.32 (1.08-1.61) |
| Khan et al,[64] 1998 | 174 | 1.32 (1.02-1.71) |
| Rickels et al,[78] 1982 | 105 | 1.35 (0.96-1.90) |
| Guelfi et al,[86] 1995 | 93 | 1.37 (0.94-1.99) |
| Croft et al,[87] 2014 | 505 | 1.38 (1.16-1.63) |
| Amsterdam et al,[88] 1986 | 109 | 1.46 (1.03-2.08) |
| Feighner et al,[89] 1989 | 33 | 1.46 (0.76-2.84) |
| Wilcox et al,[90] 1994 | 81 | 1.49 (1.00-2.21) |
| Claghorn et al,[91] 1983 | 148 | 1.51 (1.10-2.09) |
| Mynors-Wallis et al,[92] 1995 | 53 | 1.53 (0.94-2.47) |
| Georgotas et al,[93] 1982 | 33 | 1.65 (0.78-3.47) |
| Paykel et al,[94] 1988 | 100 | 1.67 (0.99-2.82) |
| Brunoni et al,[95] 2012 | 60 | 1.73 (1.11-2.70) |
| Hormazabal et al,[96] 1985 | 33 | 1.74 (0.91-3.31) |
| Versiani et al,[97] 2000 | 56 | 1.81 (1.09-3.02) |
| Cohn et al,[98] 1985 | 111 | 1.84 (1.32-2.56) |
| Feighner et al,[99] 1984 | 49 | 2.32 (1.39-3.89) |
| Rodriguez et al,[100] 2004 | 20 | 2.33 (0.73-7.49) |
| Feighner,[101] 1980 | 27 | 2.43 (1.19-4.99) |
| Shipley et al,[102] 1981 | 76 | 2.45 (1.47-4.09) |
| Mann et al,[103] 1981 | 19 | 3.08 (1.04-9.11) |
| Summary | 20 883 | 1.14 (1.11-1.17) |




Multiple comparisons with the same placebo group were used from studies appearing more than once (ie, multi-arm trials). Numbers correspond to number of participants used for each comparison. The total number of unique participants was 17 540; the total number of participants across all comparisons was 20 833 because the same placebo group was compared with several antidepressant groups in multi-arm trials. There are no years available for unpublished sources; arrows reflect 95% CIs extending beyond the graph. NA indicates year not applicable.

5 AD classes (CVRs and 95% CIs are provided in the eTable in the Supplement).

## Discussion

Our primary aim was to examine whether there is evidence of systematic variability in the symptomatic response to ADs by comparing variability in outcomes in RCTs between participants with MDD assigned to receive ADs or placebo. As hypothesized, we found that variability in responses among participants receiving ADs was 14% greater than among those receiving a placebo. This finding suggests that there may be moderators that are systematically associated with responses to ADs beyond nonspecific (placebo) effects or statistical factors (eg, random chance or measurement error).

Table 1. Results of Secondary Analyses Stratified by Baseline Depression Severity and Antidepressant Class

| Characteristic | No. of Comparisons | CVR (95% CI)[a] | *P* Value |
|---|---|---|---|
| Baseline depression severity | | | |
| Minimal | 29 | 1.13 (1.07-1.19) | <.001 |
| Midrange | 50 | 1.15 (1.11-1.19) | <.001 |
| Severe | 30 | 1.14 (1.09-1.19) | <.001 |
| Compared with midrange | | | |
| Minimal | 79 | 0.98 (0.92-1.05) | .59 |
| Severe | 80 | 0.99 (0.93-1.05) | .82 |
| AD class | | | |
| NA | 17 | 1.27 (1.16-1.39) | <.001 |
| NDRI | 10 | 1.15 (1.03-1.28) | .02 |
| SNRI | 10 | 1.20 (1.09-1.30) | <.001 |
| SSRI | 52 | 1.12 (1.08-1.16) | <.001 |
| Other AD | 23 | 1.11 (1.06-1.17) | <.001 |
| Compared with NA | | | |
| NDRI | 27 | 0.90 (0.78-1.04) | .15 |
| SNRI | 27 | 0.95 (0.84-1.07) | .36 |
| SSRI | 69 | 0.88 (0.80-0.97) | .01 |
| Other AD | 40 | 0.87 (0.79-0.97) | <.001 |

Abbreviations: AD, antidepressant; CVR, coefficient of variation ratio; NA, noradrenergic agent; NDRI, norepinephrine–dopamine reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a] The CVRs reflecting comparisons to a reference group estimate the difference in CVR (on the natural log scale) between the reference and other group. These estimates have been back-transformed, with a CVR less than 1 representing less variability than the reference group.

Table 2. Coefficient of Variation Ratios Predicted by the Mixed-Effects Model Specifying Publication Year as a Continuous Moderator for 5 Publication Years

| Publication Year | Coefficient of Variation Ratio (95% CI) |
|---|---|
| 1975 | 1.33 (1.22-1.46) |
| 1985 | 1.27 (1.19-1.35) |
| 1995 | 1.21 (1.17-1.26) |
| 2005 | 1.15 (1.12-1.19) |
| 2015 | 1.10 (1.05-1.15) |

Assuming that these moderators include individual differences, our findings provide empirical support for efforts to personalize treatments for MDD. They suggest that it may be possible to select specific ADs based on some specific characteristics of unique patients. Our findings that ADs were associated with greater variability in response than placebo could be all the more intriguing because participants in RCTs are selected to be more homogeneous than patients with MDD seen in clinical practice; in these patients with greater variability in clinical characteristics, one would expect to find even more variability in response to ADs.

Our findings contrast with the previous work in another field of psychiatry, which showed that responses to antipsychotics are not more variable than responses to placebo in patients with schizophrenia.[6] Although MDD and schizophrenia are heterogeneous conditions,[104] schizophrenia may be less heterogeneous than MDD. Furthermore, schizophrenia does not appear to be characterized by clinically useful subtypes.[105] By contrast, various MDD subtypes have been proposed based on differences in cause, symptom profile, time of onset, course, and severity.[106,107] Any of these differences could account for the variability we found in responses to ADs.

Our results support the assumption that there are meaningful moderators of responses to ADs, which we hypothesize may be associated with some unidentified subtypes of MDD. Findings from our secondary analyses suggest that traditional MDD subtypes based on symptom severity may not be reliable factors associated with this variability. This finding is interesting given that severity of depression appears to be a factor generally associated with responses to treatment.[108,109] Because the difference in response rates between ADs and placebo is highest in individuals with severe depression,[18,19,110] we expected that the variability of responses would be higher in individuals with severe depression. There may be other differences (eg, associated with symptom profile or AD mechanism of action) that contribute to this observed variability. For example, some ADs may be more effective at treating certain subtypes of depression,[15] which may correspond to specific biological or psychological individual profiles. If this possibility is true, matching specific characteristics of patients with specific ADs could increase response rates and consequently reduce variability in response.

We found some evidence that AD class affected variability in outcomes, with responses to SSRIs and drugs classified in the other AD category being less variable, compared with placebo, than responses to NAs. Findings from this secondary analysis and our post hoc analysis suggest that variability in response to ADs with noradrenergic reuptake-inhibiting properties (ie, NAs, NDRIs, and SNRIs) is higher than variability in response to ADs that affect only synaptic serotonin (ie, SSRIs). Responses to ADs that have noradrenergic effects may be more variable because they may have a greater effect on depressive symptoms compared with ADs that affect only synaptic serotonin.[111-113] Alternatively, functional unblinding in RCTs of ADs with noradrenergic effects may account for this finding. Cipriani and colleagues[20] reported that, compared with SSRIs, dropout rates due to adverse effects were generally higher for noradrenergic ADs, introducing the possibility that raters in some RCTs were unblinded to treatment allocation.

We also found that variability in responses to ADs compared with placebo was lower in RCTs published more recently. This is congruent with the finding in the study by Cipriani and colleagues[20] and other studies that have shown smaller effect sizes in more recent and larger placebo-controlled AD trials (ie, a higher placebo response and lower differences between AD and placebo). This association cannot be explained in these studies or in our analyses by the use of SSRIs in more recent AD trials. Another possibility is that the methods of AD trials have improved over time, and the higher variability in responses to ADs vs placebo is from biases in the way that older RCTs were conducted or reported (eg, small sample sizes, a lack of blinding, or biased reporting focusing on selective outcomes).

## Limitations

Our study has some limitations. The validity of our findings rests on the quality of RCTs that were included in the network meta-analysis, which in some cases was low.[20] Some RCTs did not provide end point means or SDs (some of the latter were imputed from other studies), which prevented us from being able to use all RCTs in the data set from Cipriani and colleagues[20] (Figure 1). However, our sensitivity analysis showed that the imputation of SDs did not affect our primary findings.

Our analysis was limited to the 15 drugs from the RCTs included in the original network meta-analysis[20] that were eligible for our study. We grouped ADs into classes, and it is likely that our results apply to other ADs belonging to the same class. However, it is possible that some ADs that we did not include would produce different results because of their specific mechanisms of action. There was also a large imbalance in the number of comparisons among AD classes, with fewer comparisons for the SNRIs and NDRIs.

Given that we relied on publicly available data, we were limited in the moderators of response variability that we were able to address. For instance, we could not consider prior treatment history in our analysis, which we expect would contribute to the systematic variability in outcomes we observed. Treatment-resistant patients with MDD who have already failed to respond to 1 or several ADs have a much lower rate of response to subsequent ADs[114-116] and thus less variability in response. This may explain why we found systematic variability in response to ADs, while Winkelbeiner and colleagues[6] did not find systematic variability in their analysis of antipsychotics: in most RCTs of antipsychotics, almost all participants have been exposed to antipsychotics, while RCTs of ADs include participants with a variety of prior exposure to ADs.[114]

In our secondary analysis of the moderating effect of depression severity, we did not have access to patient-level data; therefore, we averaged baseline means across conditions in each study to classify RCTs into 1 of 3 severity categories. Although these categories did not moderate response variability, it is possible that individuals were misclassified, resulting in a loss of power for this analysis. We also did not have access to item-level data; thus, we were not able to examine how various symptom types or profiles affected variability, which remains an important direction for future work. Last, different scales were used in different RCTs to capture depression severity at baseline and end point. Although 85% of RCTs used the HAMD-17 or HAMD-21, this may be an additional source of variability in this analysis.

## Conclusions

Even though our results should be replicated before they can be used to identify potential moderators of personalized AD effect, increased variability in responses to ADs compared with placebo is encouraging. Although previous efforts to identify factors associated with response to specific ADs have generally been unsuccessful,[5,12-14] our findings offer empirical support for further investigation into this line of work.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**Author Affiliations:** Centre for Addiction and Mental Health, Toronto, Ontario, Canada (Maslej, Mulsant); Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada (Maslej, Mulsant); Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine, School of Public Health, Yoshida-Konoe, Sakyo, Kyoto, Japan (Furukawa); Department of Clinical Epidemiology, Kyoto University Graduate School of Medicine, Kyoto University School of Public Health, Yoshida-Konoe, Sakyo, Kyoto, Japan (Furukawa); Department of Psychiatry, University of Oxford, Oxford, United Kingdom (Cipriani); Warneford Hospital, Oxford Health National Health Service Foundation Trust, Oxford, United Kingdom (Cipriani); Department of Psychology, Neuroscience & Behaviour, McMaster University, Hamilton, Ontario, Canada (Andrews).



**Author Contributions:** Dr Maslej had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
*Concept and design:* Maslej, Cipriani, Mulsant.
*Acquisition, analysis, or interpretation of data:* All authors.
*Drafting of the manuscript:* Maslej, Mulsant.
*Critical revision of the manuscript for important intellectual content:* All authors.
*Statistical analysis:* Maslej, Cipriani.
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*Supervision:* Cipriani, Mulsant.

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