Original Paper

Direct comparison of tricyclic and serotonin-reuptake inhibitor antidepressants in randomized head-to-head trials in acute major depression: Systematic review and meta-analysis

Journal of Psychopharmacology
2017, Vol. 31(9) 1184–1189

DOI: 10.1177/0269881117711709
journals.sagepub.com/home/jop

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Abstract

Background: A comparison across trials conducted over several decades suggested superior efficacy of tricyclic antidepressants (TCAs) over selective serotonin-reuptake inhibitors (SSRIs). However, this outcome may reflect a selective secular decline of responses after randomization to placebo. Remaining uncertainty encouraged direct comparison of the drug-types in trials involving randomized, head-to-head comparisons.

Methods: We systematically identified reports of randomized trials of TCAs versus SSRIs for major depression in several digital databases, and applied standard meta-analytic and multiple-factor regression methods to analyze and pool the findings.

Results: In 89 head-to-head trials, there was no detectable overall difference in responder rates or percent-improvement between TCAs and SSRIs. In addition to non-difference between drug-types, outcomes were unrelated to reporting-year, trial-size or nominal duration, proportion of women participants, initial depression ratings, rating scales, subjects/arm, imipramine-equivalent mg/day drug dose, or dropout rate. Trial size and duration increased significantly over the years 1980–2016.

Conclusions: Previous evidence suggesting superior benefits of TCAs over SSRIs for the treatment of acute major depression is probably an artifact of a selective secular decline in responses to placebo, as no difference was found in a large series of direct comparisons of these antidepressant-types.

Keywords

Antidepressants, head-to-head, randomized trials, serotonin-reuptake inhibitor, tricyclic

Introduction

Selective serotonin-reuptake inhibitor (SSRI) antidepressants have come to dominate the antidepressant market since the early 1990s (Baldessarini, 2013). Initially, there were some uncertainties about their relative efficacy compared with older, standard agents, notably tricyclic antidepressants (TCAs). Several earlier reviews proposed that the antidepressant efficacy of these drug types was indistinguishable (Anderson, 2000; Arroll et al., 2005; Freemantle et al., 2000; Kasper et al., 1992; MacGillivray et al., 2003; Song et al., 1993; Steffens et al., 1997). In a more recent review of randomized, placebo-controlled trials of antidepressants reported since 1980, we found that SSRIs appeared to be significantly less effective than TCAs (Undurraga and Baldessarini, 2012). That impression may have been an artifact of selective decreases in response rates among depressed subjects randomized to placebo-treatment, whereas responses to active drugs showed little change over the past several decades (Furukawa et al., 2016; Schalkwijk et al., 2014; Undurraga and Baldessarini, 2012). Since many trials of TCAs were carried out earlier than trials of SSRIs, these circumstances may give TCAs an artifactual appearance of superiority.

Aims of the study

Given remaining uncertainties, the objective of this study was to compare the efficacy of TCAs and SSRIs for acute major depression in an up-to-date, systematic review of the available research involving head-to-head, direct comparisons of SSRIs and TCA-like antidepressants in the same randomized, blinded trials, reported between 1980 and 2016. Our primary hypothesis was that there would be little difference between the antidepressant types based on direct comparisons under matched conditions. Secondary hypotheses were that within-trial improvements in depression ratings among depressed participants randomized to a TCA or an SSRI would not show evidence of significant secular changes over the observed reporting years, but that the size of trials (subject count) and their duration would increase, and that SSRIs might be associated with lower dropout rates. Study

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outcomes were expected to bear on clinical decisions of which type of antidepressant to try first.

Methods

Search strategy

We carried out a systematic, computerized search of the Medline, CINAH Library, Cochrane Library, Embase, and PsycINFO research literature databases, using the following search-terms: "depressive disorder AND antidepressant or citalopram or escitalopram or fluoxetine or fluvoxamine or paroxetine or sertraline or zimelidine AND clomipramine or amineptine or amitriptyline or desipramine or dothiepin or doxepin or imipramine or lofepramine or maprotiline or mianserin or nomifensine or nortriptyline". In addition, we hand-searched published reviews and research reports for additional, relevant citations. The search was limited to peer-reviewed, randomized, double-blind, controlled trials lasting ≥4 weeks, in acute episodes of adult major depression diagnosed by standardized criteria specified below. We limited the search to trials published from 1980 through May 2016 in any language, with an English or Spanish summary.

Eligibility criteria

Included were reports of double-blind, head-to-head trials involving randomization to monotherapy involving at least one TCA versus one SSRI, in adults in an acute, apparently unipolar, major depressive episode based on DSM-III-to-5, ICD-9 or -10, or RDC diagnostic criteria, and with at least 20 subjects per treatment arm.

Antidepressant doses could be fixed or flexible. Total average daily drug doses were converted to approximate imipramine-equivalents (IMI-eq mg/day) (Baldessarini, 2013) to support comparisons of agents of dissimilar potency. We excluded reports involving special populations, such as juvenile or geriatric patients, those with major general medical or neurological conditions, or including ≥10% with bipolar depression (with uncertain antidepressant responses (Pacchiarotti et al., 2013)), dysthymia, or other diagnoses.

Outcome measures

We pre-selected two primary efficacy measures, based on our previous review (Undurraga and Baldessarini, 2012): (a) categorical percent responding, defined in most cases as ≥50% reduction in initial depression rating-scale scores by a last observation. Depressive symptom severity was scored with standard rating scales: Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960); Montgomery–Åsberg Depression Rating Scale (MADRS (Montgomery and Åsberg, 1979)); Clinical Global Impression (CGI (Guy, 1976)); or Beck Depression Inventory (BDI (Beck et al., 1961)); (b) percent-improvement in measures of change in within-subject depression ratings to the point of last assessment. For some analyses, such as assessment of secular changes, we expressed initial depression severity as the percentage of the maximum attainable score so as to adjust for differences in scoring with different rating scales. When multiple outcome measures were reported, we used those based on HDRS ratings.

We also considered factors that might influence outcomes, including numbers of subjects and collaborating sites, percentage women, IMI-eq daily drug doses, trial-duration, dropout rates, and year of reporting, as well as specific drugs and types. As manufacturers of the drugs involved sponsored almost all trials, sources of support were not further considered.

Data analysis

The primary assessment was comparable efficacy of SSRIs versus TCAs, based on random-effects meta-analyses with relative responder rates (RRs) or standardized mean difference (SMD) in percent-improvement with a SSRI versus a TCA in each included trial. SMD relied on reported standard deviation (SD) or estimates based on overall variance among TCA trials and SSRI trials. We also used metaregression modeling to test for independent and significant effects of selected factors on outcome measures. Secondary analyses included bivariate linear regression or Spearman's rank-correlation (r_s) analyses of selected trial characteristics versus reporting years to test for secular changes. Paired *t*-tests were used to compare selected measures for within-trial differences between participants treated with a TCA versus a SSRI. Data are reported as means ± standard deviation (SD) or with 95% confidence intervals (CIs). Statistical significance required two-tailed *p*-values <0.05. Data analyses employed Statview-5 (SAS Institute; Cary, NC, USA) spreadsheets for data-management, and STATA-13 statistical software (StataCorp; College Station, TX, USA).

Results

Characteristics of trials included

We identified a total of 89 peer-reviewed reports (online supplementary appendix, references A1–A89) of randomized trials of SSRIs versus TCAs for acute major depression that met our inclusion/exclusion criteria, with results of the document-selection process summarized according to PRISMA criteria (Moher et al., 2009) (online supplementary appendix Figure A1). They involved a total of 15,435 patient-participants (8002 with SSRIs, 7433 with TCAs). There was an average of 90 (SSRI) to 84 (TCA) subjects/cell in an average of 7.7 collaborating sites/trials lasting 6.3 (range: 4–12) weeks (online supplementary appendix Table A1, and Table 1). Doses (IMI-eq mg/day) of the 18 antidepressants encountered were closely matched among SSRIs (173 (CI: 157–189)) and TCAs (161 (CI: 148–175)). Most of the trials were reported in the 1990s (53.9%), followed by the 1980s (32.6%), the 2000s (12.4%), and very few after 2010 (1.12%). Depression rating scales used were: HDRS 88.8%, MADRS 7.87%, CGI 2.25%; or BDI 1.12%. Data for meta-analyses of SMDs were provided by 81 trials, and for relative RRs by 57 trials (online supplementary appendix Table A1).

We evaluated several factors for potential secular changes over the years of study-reports (1982 to 2015), including: subjects/trial or per trial-arm, collaborating sites/trial, nominal trial duration (weeks), IMI-eq (mg/day) average drug dose, initial depression severity (as % of scale maximum), proportion of subjects considered responders (usually at ≥50% improvement in depression ratings), mean %-improvement in depression ratings,

Table 1. Characteristics of randomized trials of TCAs versus SSRIs for major depression.

Measure	Means (95% CI)			TCA *vs*. SSRI *p*-value (paired-*t*)	Regression slopes (β) *vs*. years (95% CI)		
	All Rx	TCAs	SSRIs		All Rx	TCAs	SSRIs
Subjects, *N*	86.7 (73.3–100)	83.5 (66.1–101)	89.9 (69.2–111)	0.160 (1.42)	2.69[a] (0.75 to 4.64)	2.32 (–0.08 to 4.70)	3.06 (–0.07 to 6.19)
Sites, *n*	10.1 (5.5–14.6)	---	---	---	0.280 (–0.20 to 0.76)	---	---
Trial duration, weeks	7.9 (5.5–10.3)	---	---	---	0.085[b] (0.03 to 0.14)	---	---
Dose, IMI-eq, mg/day	167 (157–178)	161 (148–175)	173 (158–189)	0.221 (1.23)	–1.67 (–3.40 to 0.06)	–0.608 (–2.91 to 1.69)	–2.74[c] (–5.35 to –0.13)
% Initial, max score	54.5 (51.6–57.4)	54.3 (51.4–57.2)	54.6 (51.7–57.5)	0.244 (1.17)	0.029 (–0.38 to 0.32)	0.059 (–0.56 to 0.44)	0.001 (–0.50 to 0.50)
Responders, %	57.0 (54.0–60.0)	57.2 (53.0–61.3)	56.8 (52.5–61.2)	0.965 (0.044)	0.111 (–0.39 to 0.61)	0.186 (–0.52 to 0.90)	0.040 (–0.69 to 0.77)
Improvement, %	52.5 (49.8–55.2)	52.4 (49.6–55.1)	52.6 (50.0–55.2)	0.816 (0.234)	0.118 (–0.21 to 0.45)	0.200 (–0.28 to 0.68)	–0.032 (–0.42 to 0.49)
All-cause, dropouts, %	26.4 (24.0–28.0)	28.1 (24.5–31.7)	24.7 (21.6–27.8)	0.021 (2.36)	–0.227 (–0.70 to 0.24)	0.092 (–0.81 to 0.63)	0.362 (–0.98 to 0.25)

Initial depression rating = percent of maximum scale score. Note that only dropout rate higher with TCAs *vs*. SSRIs is significant; [a]t=2.73, p=0.007; [b]t=3.09, p=0.003; [c]t=2.08, p=0.04; no other change over years was significant, nor did any secular change differ between antidepressant-types.
CI: confidence interval; IMI-eq: imipramine-equivalent; Rx: treatments; SSRI: selective serotonin-reuptake inhibitor; TCA: tricyclic antidepressant.

Table 2. Meta-analyses of head-to-head trials comparing TCAs with SSRIs.

Outcome	Trials *n*	Pooled value	95% CI	*z*-score	*p*-value
Improvement, SMD	81	0.019	–0.138 to 0.177	0.24	0.808
Responders, RR	57	1.03	0.974 to 1.09	1.04	0.300
Number-needed-to-treat	57	72.6	23.8 to ∞	0.96	0.338

Based on random-effects meta-analysis.
CI: confidence interval; RR: relative responder-rate; SMD; standardized mean difference; SSRI: selective serotonin-reuptake inhibitor; TCA: tricyclic antidepressant.

and dropout rates for all causes (Table 1). Of these measures, only the number of subjects/trial and the duration of trials increased significantly over time. In addition, there was a small, but significantly higher, overall dropout rate with TCAs (28.1%) than with SSRIs (26.4%; Table 1).

Outcomes

The primary aim of this study was to compare measures of efficacy in TCA versus SSRI treatment arms of head-to-head comparison trials, based on random-effects meta-analysis with outcomes as SMDs in improvements with each drug-type and on the ratio of RRs for SSRIs/TCAs (Table 2). Both meta-analytic procedures indicated highly significant heterogeneity in outcomes among trials (heterogeneity I^2 for SMD = 1688, for RR = 127; both $p<0.0001$), encouraging use of random-effects modeling. By both outcomes, there were very small, non-significant, differences in responses between drug-types (3.0% difference in RR (online supplementary appendix Figure A2) and 1.9% difference in SMD). In addition, an estimated number-needed-to-treat based on the reciprocal of the difference in responder rates was very large (73 subjects to gain superiority of an SSRI over a TCA), again indicating very little difference in short-term efficacy of the two classes of standard antidepressant drugs. Based on a power estimate assuming false positive rate of 0.05 and false negative rate of 0.20, it would require only about 38 comparisons to detect a difference of only 5% in clinical response between SSRIs and TCAs (55% *vs*. 50%).

We also considered factors of interest for relationships to outcomes, using meta-regression analysis. Response was unrelated to reporting-year, trial-size or nominal duration, proportion of women participants, initial depression ratings (as % of maximum possible scale score), rating scale employed, mean IMI-eq mg/day drug dose, or mean early dropout rate (Table 3). However, trial duration (weeks; Spearman's r_s = 0.435, $p<0.0001$) and size (subjects/trial arm; r_s = 0.332, p=0.002) and duration increased highly significantly over the years 1980–2016 (see also Table 1). Inspection of funnel plots from meta-analyses (1/effect size *vs*. standard error of effect size) indicated symmetrical distribution of data, and did not suggest the presence of reporting bias.

Finally, we compared responder rates and percent-improvement ratings for each of the 18 specific drugs tested (Table 4). The overall benefits of both types of drugs, again, were very

Table 3. Metaregression modeling.

Covariate	Slope (95% CI)	*z*-score	*p*-value
Percent female subjects[a]	+0.0056 (–0.00017 to +0.011)	1.90	0.06
IMI-eq dose, mg/day[a]	+0.00094 (–0.00044 to +0.0023)	1.33	0.18
Initial depression severity[a,b]	+0.0033 (–0.0023 to +0.0089)	1.15	0.25
Subjects/trial arm, *n*	+0.00056 –(0.00041 to +0.0015)	1.14	0.25
Trial duration, weeks	+0.0135 (–0.020 to +0.047)	0.80	0.42
Dropout rate[a]	–0.0016 (–0.0056 to +0.0025)	0.76	0.45
Reporting year	+0.0027 (–0.010 to +0.016)	0.41	0.68
Diagnostic criteria	+0.0018 (–0.038 to +0.041)	0.09	0.93
Collaborating sites, *n*	+0.00066 (–0.0184 to +0.0197)	0.07	0.95
Rating scale used	+0.0051 (–0.456 to +0.467)	0.02	0.98

[a]Mean of trial selective serotonin-reuptake inhibitor and tricyclic antidepressant treatment arms.
[b]Percent of rating scale maximum score.
Metaregression based on standardized mean difference also confirmed a lack of association with these measures and outcome.
CI: confidence interval; IMI-eq: imipramine-equivalent.

similar (mean of 52.5% responding, and a mean improvement of 57.0%), with an expected highly significant correlation of the two outcome measures across drugs (r=0.657, p<0.0001). Given the similar responses for both antidepressant types and the limited number of trials/drug (for percent-improvement as outcome, mean: 7.8 (CI: 5.1–10.5) trials/drug), it is not surprising that there were no significant differences among drugs in rates of response or improvement (Table 3). Based on percent-improvement and agents with at least 10 trials, the nominally highest mean response was found with clomipramine (63.5%), and lowest with imipramine (47.5%), underscoring the relatively narrow range of levels of response across specific drugs (Table 4). Also, among six agents with >10 trials (mean = 20.5±6.1 trials/drug), again, there was no difference in percent-improvement (t=1.07, p=0.341; Table 4).

Discussion

This study compared clinical responses as responder-rates and percent-improvement in 89 randomized, head-to-head comparisons of a SSRI versus a TCA given to treat acute major depression in adults, reported between 1980 and 2016 and identified by systematic literature searching. We aimed to follow up findings in our previous meta-analytic review of controlled trials of antidepressants versus placebo reported since 1980 (Undurraga and Baldessarini, 2012). It found evidence of a greater average response to TCAs than to SSRIs—contrary to earlier findings based on meta-analyses of such trials (Arroll et al., 2005; Freemantle et al., 2000; Kasper et al., 1992; MacGillivray et al., 2003; Song et al., 1993; Steffens et al., 1997; Undurraga and Baldessarini, 2012) and to an earlier, highly inclusive, meta-analysis of head-to-head trials (Anderson, 2000). Possibly greater antidepressant efficacy of TCAs would accord with observations indicating that risk of excessive mood-elevation or switching in adults from depression to mania or hypomania may be greater with TCAs than SSRIs (Tondo et al., 2010). We suspected that the finding of significant superiority of TCAs based on meta-analysis of studies dating to the 1980s may have been an artifact associated with a selective but variable secular decline in responses in placebo-arms, but not drug-arms, of antidepressant trials in recent decades since the 1980s, with a greater proportion of trials of TCAs over SSRIs in earlier years (Furukawa et al., 2016; Schalkwijk et al., 2014; Undurraga and Baldessarini, 2012).

The primary outcome of the present study, based on random-effects meta-analyses, was of virtually no difference between drug-types in relative responder-rates (RRs) or percent-improvement (SMD) (Table 2). Additional, secondary, findings included a significantly higher all-cause dropout rate with TCAs than with SSRIs, as well as secular increases in the number of subjects/trial and duration of trials over the years sampled (Table 1). In metaregression modeling, the only factor associated significantly and independently with greater percent-improvement was lower dropout rate, or greater retention in trials (Table 3). The finding that both types of antidepressants had similar efficacy but that TCAs were associated with more dropouts and perhaps lesser tolerability supports clinical selection of SSRIs over TCAs as a first choice in the treatment of acute major depression. Finally, within limits of available trials, there were no significant differences in responses associated with any specific agent (Table 4).

The primary study outcome appears to represent a straightforward indication of a lack of difference in efficacy of SSRIs and TCAs within the range of clinical types of depression encountered in modern controlled trials. Such a conclusion, based on head-to-head comparisons, accords with earlier reviews addressing the same question (Anderson, 2000; Arroll et al., 2005; Freemantle et al., 2000; Kasper et al., 1992; MacGillivray et al., 2003; Song et al., 1993; Steffens et al., 1997). However, the lack of apparent difference in outcomes pooled across 89 randomized, head-to-head trials may not prove equal efficacy if within- and between-trial variance limits detection of relatively small differences. Although within-trial comparisons of the antidepressant types involved nominally identical conditions, it is likely that a range of clinical types was included. Indeed, contemporary concepts of "major depression" represent a variety of clinical types, including severe or mild, neurotic-anxious, melancholic, agitated, psychotic, dysthymic, or undiagnosed bipolar types, which can vary in response to antidepressants (Baldessarini, 2013; Bühler et al., 2014; Yang et al., 2013). Another source of heterogeneity is differences in the diagnostic criteria used. Such clinical heterogeneity might contribute to an

Table 4. Responses to specific antidepressants.

Drug	Symbol	Type	% Responding (*n* trials)	% Improvement (*n* trials)
Clomipramine	CMI	TCA	60.6±6.87 (6)	63.5±8.82 (8)
Nortriptyline	NTP	TCA	57.3±15.2 (3)	61.0±12.0 (4)
Citalopram	CTP	SSRI	58.5±22.1 (4)	60.6±7.44 (4)
Escitalopram	*s*CTP	SSRI	70.0 (1)	57.7 (1)
Zimelidine	ZML	SSRI	60.0±2.83 (2)	57.1±10.3 (2)
Doxepin	DOX	TCA	61.1 (1)	54.1±9.33 (2)
Amitriptyline	AMI	TCA	66.8±14.9 (17)	53.8±13.0 (23)
Dothiepin	DTP	TCA	61.6±16.5 (2)	53.7±8.50 (5)
Paroxetine	PRX	SSRI	57.7±18.5 (16)	53.7±10.1 (20)
Fluoxetine	FLX	SSRI	59.2±17.5 (18)	53.3±13.7 (27)
Desipramine	DMI	TCA	62.0 (1)	53.1±16.5 (3)
Mianserin	MIA	TCA	48.4 (1)	51.5±13.2 (2)
Maprotiline	MPT	TCA	56.6±23.1 (6)	51.1±15.5 (7)
Sertraline	SRT	SSRI	58.1±8.35 (9)	50.4±5.48 (10)
Fluvoxamine	FLV	SSRI	46.0±17.0 (9)	49.0±13.5 (18)
Imipramine	IMI	TCA	48.7±14.0 (18)	47.5±11.2 (25)
Lofepramine	LFP	TCA	48.0±8.56 (2)	44.4±5.16 (2)
Amineptine	ANP	TCA	36.0 (1)	31.8 (1)
Mean, *n*=18 (95% CI)	---	---	**52.5** (50.7–54.3)	**57.0** (54.0–60.0)

Data are in descending order by percent-improvement. Improvement and response rates are closely correlated (r=0.657, p<0.0001) and their averages are similar. Differences among specific drugs are not significant for responder rate (t=1.09, p=0.295) or percent-improvement (t=1.14, p=0.198). Further analysis of six drugs with ≥10 trials each (mean 20.5±6.1 trials/drug) found no significant difference in percent-improvement (t=1.07, p=0.341) among AMI, FLX, FLV, IMI, PRX and SRT.
TCA: tricyclic antidepressant; SSRI: selective serotonin-reuptake inhibitor; CI; confidence interval.

apparent lack of differentiation by drug-type within trials. Additional heterogeneity is likely to arise in pooling data across trials, as in meta-analysis. Overall, heterogeneity within and between trials is likely to contribute to findings of apparent "no difference", including effects of regression to mean outcomes. With striking consistency, meta-analytic averaging has encountered difficulties in demonstrating differences in efficacy between specific drugs within classes of psychotropic agents (antidepressants, antipsychotics, antimanics), as is reflected in largely overlapping confidence intervals among responses associated with particular agents (Baldessarini, 2013; Leucht et al., 2013; Undurraga and Baldessarini, 2012; Yildiz et al., 2015).

Given these concerns, we attempted to exclude trials with dissimilar types of patients (e.g. with bipolar or dysthymic depression, juvenile or geriatric subjects, and those with various co-morbid conditions) and limited inclusion to trials of substantial size, using standard diagnostic and assessment methods, and lasting 4–12 weeks. Even with such relatively selective inclusion criteria, substantial within-trial and between-trial variance and sample heterogeneity remain likely. Nevertheless, statistical power considerations indicate that a sample of 89 comparisons should be adequate to detect differences in clinical response as small as 5%. That is, it seems likely that average differences in efficacy between SSRIs and TCAs in controlled trials are negligible for groups of subjects diagnosed with major depression. Whether specific subtypes of major depression patients, such as severely depressed, psychotic, or hospitalized patients, may respond selectively to one or another drug type remains to be tested adequately (Baldessarini, 2013).

Limitations

This study is limited to randomized trials with head-to-head comparisons of an SSRI versus a TCA for acute major depression that have undergone peer-review and publication. Even among the substantial number of trials meeting inclusion and exclusion criteria designed to limit sample heterogeneity and variability of conditions within and between trials, effects of heterogeneity might tend to obscure possible differences. Moreover, not all reports included all measures of interest.

Conclusion

Despite these potential limitations, the primary findings add strong support to the conclusion that differences in efficacy between SSRIs and TCAs among broadly sampled trial participants meeting contemporary diagnostic criteria for a major depressive episode were small or negligible. We also found that all-cause dropout rates were significantly higher with TCAs than SSRIs, suggesting gains in tolerability with the modern agents. Finally and unsurprisingly, efficacy was greater with lower dropout rates.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was

supported by CONICYT (grant numbers FONIS 2016 ID: SA15I2 0058, Interdisciplinary Research Program CONICYT PIA ACT1414; FONDECYT ID: 1160736), Clínica Alemana de Santiago (Research Grant to JU); the Bruce J Anderson Foundation and the McLean Private Donors Psychopharmacology Research Fund (to RJB).

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