

ANTIDEPRESSANT USE BY CLASS: ASSOCIATION WITH MAJOR ADVERSE CARDIAC EVENTS IN
PATIENTS WITH CORONARY ARTERY DISEASE

BRIEF TITLE: ANTIDEPRESSANT USE IN CAD PATIENTS AND MACE

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Abstract

Background: To assess use of antidepressants by class in relation to cardiology practice recommendations, and the association of antidepressant use with the occurrence of major adverse cardiovascular events (MACEs) including death.

Methods: Historical cohort study of all patients who completed cardiac rehabilitation (CR) between 2002-2012 from a major CR center. Participants completed the Patient Health Questionnaire (PHQ-9) at the start and end of the program. A linkage system enabled ascertainment of antidepressant use and MACEs through 2014.

Results: There were 1694 CR participants, of which 1266 (74.7%) completed the post-program PHQ-9. Depressive symptoms decreased significantly pre (4.98 ± 5.20) to post (3.57 ± 4.43) program ($p < .001$). Overall, 433 (34.2%) participants were on antidepressants; most often selective serotonin reuptake inhibitors (SSRIs; $n=299$; 23.6%). Proportion of days covered was approximately 70% for all four major antidepressant classes; discontinuation rates ranged from 37.3% for tricyclics to 53.2% for serotonin-norepinephrine reuptake inhibitors (SNRIs).

Antidepressant use was significantly associated with lower depressive symptoms post-CR (pre 7.33 ± 5.94 vs post 4.69 ± 4.87 , $p < .001$). After a median follow-up of 4.7 years, 264 (20.9%) participants had a MACE. After propensity-matching based on pre-CR depressive symptoms among other variables, participants taking tricyclics had significantly more MACEs than those not (hazard ratio [HR]=2.46; 95% confidence interval [CI]=1.37-4.42); as well as those taking atypicals versus not (HR=1.59; 95%CI=1.05-2.41); and SSRIs (HR=1.45; 95%CI=1.07-1.97). There was no increased risk with use of SNRIs (HR=0.89; 95% CI=0.43-1.82).

Conclusion: Use of antidepressants was associated with lower depression, but use of all antidepressants except SNRIs was associated with more adverse events.

Keywords: depression, coronary artery disease, antidepressants, mortality, cardiac rehabilitation

Introduction

Cardiovascular diseases (CVDs) are the leading cause of mortality worldwide[1,2] and depression is the second leading cause of disability worldwide.[3] The conditions are highly comorbid,[4] with depression being approximately three times more common in patients after an acute myocardial infarction than in the general community.[5] It has been estimated that 30% of patients who have been hospitalized for a myocardial infarction experience increased depressive symptoms, and 15-20% suffer from major depression. Depression in patients who have CVD is associated with less adherence to secondary prevention treatments, poor health-related quality of life, and higher rates of adverse events, including mortality rates that are twice as high than those without depression.[6,7]

Accordingly, the American Heart Association[8] recommends screening for depression in cardiac patients using the Patient Health Questionnaire (PHQ).[9] Assessment of depressive symptoms[10,11] is considered a core component of cardiac rehabilitation (CR) by many professional Societies. [12–15] When depression is detected and formally diagnosed, the American Heart Association also recommends appropriate treatment with cognitive-behavioral therapy and/or antidepressants.[8]

Given trial evidence of efficacy to reduce depression and presumed safety,[16] Selective Serotonin Reuptake Inhibitors (SSRIs) are the recommended antidepressant class for first-line pharmacologic therapy in CVD patients,[17] and atypical antidepressants as second-line therapy. Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) are also recommended as second-line therapy, however they have not been studied in CVD patients.[17] Tricyclic antidepressants

(TCAs) are not recommended in many patients with CVD, particularly among those with coronary artery disease (CAD) or ventricular arrhythmias, due to their documented arrhythmogenic effects.[18] Research in CVD populations have shown that use of pharmacologic antidepressant therapy is associated with moderate reductions in depression, but does not necessarily reduce cardiovascular events or deaths in the context of comorbid depression.[5,16,19–21] However, no studies to our knowledge have examined the association between antidepressant class and long-term outcomes in CAD patients. There is also paucity of data assessing current patterns of antidepressant use by class and current clinical practice recommendations, and patients' adherence.

Accordingly, the objectives of this study were to describe and assess in a cohort of CAD patients participating in CR: (1) antidepressant use by class, in relation to clinical practice recommendations, (2) patients' adherence with pharmacologic antidepressant treatment, and (3) the association between antidepressant use by class and the occurrence of major adverse coronary events (MACEs) including death.

Materials and Methods

Design and Data Sources

This was an observational, community-based, retrospective cohort study. Patients with CAD who entered the Mayo Clinic CR program in Rochester, Minnesota between the years of 2002 and 2012 comprised the cohort. Clinical data from CR intake assessments were extracted. Patients were administered the PHQ-9 pre and post-program.

Medication and MACEs were ascertained through record linkage with the Rochester Epidemiology Project through to December 2014.[22] This population-based record linkage system electronically stores the clinical information developed by the Mayo Clinic with that obtained by other community providers, the Olmsted Medical Group and the affiliated Olmsted Community Hospital, that have provided research authorization to the state of Minnesota.[23] Follow-up data was complete for this cohort. The study protocol was approved by both the Mayo Clinic and Olmsted Medical Center Institutional Review Board.

Setting

Residents of Rochester or Olmsted County, Minnesota, and the surrounding area are relatively distant from other large metropolitan health care institutions, and the Mayo Clinic CR program was the only CR program in the county during the study period. The outpatient CR program is 12 weeks in duration, and is based on the American Association of Cardiovascular and Pulmonary Rehabilitation guidelines.[12] All patients are encouraged to attend group stress management sessions; here, a video is presented which describes how stress affects the body, and techniques such as relaxation, exercise, and deep breathing. Patients are also provided videos to take home demonstrating relaxation, tai chi /qigong, and mindfulness-based approaches to stress management.

The PHQ-9 is administered routinely to all patients at CR intake and discharge assessments.[9] The staff discusses results with patients. Patients with pre-CR scores $\geq$ ten are considered for referral to psychology; patients expressing suicidal ideation are provided an emergency

consultation. Primary care and/or mental health providers may then prescribe pharmacotherapy or other treatments.

Participants

Inclusion criteria were patients 18 years of age or older, with a documented diagnosis of CAD, who attended the CR program. CAD was defined as: (1) a previous myocardial infarction (ST or non-ST-segment elevation), (2) stable or unstable angina, and/or (3) previous revascularization by either coronary artery bypass grafting or percutaneous coronary intervention. In order to facilitate outcome assessment, an additional inclusion criterion was that patients were to be residents of Olmsted County, Minnesota. Patients who did not complete the pre- or post-CR PHQ-9 were excluded. Thus included patients completed the CR program.

Measures

Most participant characteristics were obtained from the record linkage system. The date of CR intake was defined as the index date. Smoking history was obtained from the electronic medical record, based on self-report to a healthcare provider.

Medications were also available through the record linkage system. Psycho-pharmacological medications were extracted from 2001 to the end of 2014. Variables were computed to categorize medication class. Anti-depressant categories were five-fold: SSRIs, SNRIs, TCAs, atypicals, and others (e.g., MAOIs). Trazodone was included as an atypical herein, but can also be considered a Serotonin Antagonist and Reuptake Inhibitor or tetracyclic. Other psycho-pharmacological medications were also categorized (e.g., benzodiazepines, antipsychotics).

Proportion of days covered was also computed (i.e., proportion of days in the measurement period the participant had filled a prescription for the medication, which is an indicator of medication adherence) using a validated approach.[24,25]

Independent Variable

The PHQ-9 is a multi-purpose instrument for screening, diagnosing, monitoring and measuring the severity of depression,[9] recommended for administration in cardiac samples.[8] The tool assesses the criteria on which the diagnosis of depressive disorder is based.[26] Response options for each item range from zero “not at all” to three “nearly every day”. It yields both a provisional depression diagnosis and a severity score.[9]

PHQ-9 total scores range from 0 to 27. Cut-points of 5, 10, 15, and 20 represent the thresholds for mild, moderate, moderately severe, and severe depression, respectively.[27] A single cut-point is currently recommended at a score of 10 or greater (i.e., “elevated” symptoms), as this has a sensitivity for depression of 88%, a specificity of 88%, and a positive likelihood ratio of 7.1.[9] The minimal clinically important difference used for the analysis was five points or greater.[28] Major depression is considered if five or more of the nine depressive symptom criteria have been present at least “more than half the days” (response option 2) in the past 2 weeks, and one of the symptoms is depressed mood or anhedonia.

Dependent Variables

MACEs were ascertained using the record linkage system from the Rochester Epidemiology Project, and included any of the following events: acute coronary syndrome (myocardial

infarction [International Classification of Diseases-9, 410·x] or unstable angina [International Classification of Diseases-9, 411·x]), coronary revascularization (coronary artery bypass grafting [Current Procedural Terminology /International Classification of Diseases-9 337700-337735/V45·81] or percutaneous coronary intervention [Current Procedural Terminology /International Classification of Diseases-9 2980-92982/V45·82]), ventricular arrhythmias that required in-hospital management (International Classification of Diseases-9 427·X),[29] or death from any cause. Mortality information was obtained directly from the Rochester Epidemiology Project, which records vital status from state vital statistics offices and the National Death Index.[30]

All outcome information was followed passively, through electronic ascertainment using diagnosis codes (an approach which has been validated).[22,23] A physician-investigator/co-author (JMI), who was blinded to baseline characteristics, reviewed a fraction of the records in the record-linkage system to confirm the outcome and validate the research strategy.

Additionally, a random 10% of the outcomes were reviewed in duplicate by a masked clinician expert/senior author (FLJ) to ascertain inter-observer agreement. It was within the excellent range ($\kappa=0.89$).

Statistical analyses

First, the differences in sociodemographic and clinical characteristics of participants who were retained post-CR (i.e., completed PHQ-9 post-program) versus those who did not complete the post-CR PHQ-9 were compared using t-tests or chi-square, as appropriate. Changes in depressive symptoms from pre-to post-CR were tested using a paired t-test (continuous measure), and chi-

square test (for severity categories). The association between depressive symptoms and antidepressant use was tested using t-tests, both independent samples (at pre and post-CR) and paired (change in depressive symptoms from pre to post-CR by antidepressant use, including by class). The association between antidepressant adherence and depressive symptoms was tested with Pearson's correlations, and between antidepressant adherence and MACEs was tested with t-tests.

The association between antidepressant use, overall and by class, with MACE was first tested at a bivariate level using chi-square analyses. To adjust for confounders that may determine either the likelihood to be placed on an antidepressant or to suffer MACE, we used a propensity matching approach. Given the sample size herein, this is considered to be a more robust approach and provide a less-biased estimator, than building a traditional multivariate regression model with confounders as predictors.[31] The nearest neighbor propensity score matching algorithm was applied, with a 2:1 matching ratio, using the following variables: age, sex; pre-CR depressive symptoms (i.e., PHQ-9 scores), body mass index, hypertension, dyslipidemia, smoking status; previous percutaneous coronary intervention or bypass surgery, or heart failure; comorbid stroke, lung disease, kidney disease, peripheral vascular disease, cancer, or diabetes. Kaplan-Meier curves and Cox regression models were created to test the association between a matched participant's use or non-use of each antidepressant within each class, and the likelihood of MACEs including death, in the propensity-matched samples. The log-rank test was used to test for difference in survival. $P > .05$ was considered statistically significant. These analyses were undertaken with the statistical package R 3.3.1.

Role of the funding source

The study sponsors played no role in the study design, data or writing of the manuscript; they also played no role in the decision to submit the paper for publication.

Results

Respondent Characteristics

Overall, 1694 patients initiated CR during the period of study, of which 1266 (74.7%) completed the follow-up PHQ-9 and comprised the sample. Their characteristics are shown in Table 1. As shown, retained participants did not differ with regard to sociodemographic characteristics from those who did not complete the follow-up PHQ-9, although they were more likely to have a history of several comorbidities, and smoking. Moreover, retained participants had significantly higher depressive symptoms pre-CR and were more likely to be taking any antidepressant than those who did not complete the follow-up assessment.

Depressive Symptoms

Mean depressive symptom scores, severity categorizations and diagnoses based on the PHQ-9 scores pre- and post-CR are shown in Table 2. As shown, most participants scored in the minimal range pre and post-CR. All depressive symptom indicators decreased significantly from pre to post-CR.

Overall, 220/1266 (17.4%) participants scored in the “elevated” range pre-CR (i.e., ≥ 10), and 125/1266 (9.9%) at post-test. Participants were categorized based on scoring above or below ten on the PHQ-9 both pre-and post-CR. Results showed that 984/1266 (77.7%) remained

subclinical (i.e. <10) throughout CR, 115/1266 (9·1%) went from elevated to subclinical, 46/1266 (3·6%) went from subclinical to elevated, and 49 (3·9%) remained elevated.

Of participants with elevated depressive symptoms pre-CR, their mean PHQ-9 score post-CR was $7·30 \pm 6·36$ (standard deviation). In most participants (983, 77·6%) PHQ-9 scores did not change at follow-up, when using a cutoff of five as the minimal clinically important difference, but for 204 (16·1%) participants their scores decreased at least five points and for 79 (6·2%) their scores increased at least five points.

Antidepressant Use

Overall, 446 (35·2%) participants were taking any psycho-pharmacological medication at any point during the period of the study, of which 433 (34·2%) were on antidepressants, and 118 (9·3%) were taking more than one antidepressant, with a median of two drugs per patient.

Class of antidepressant used is shown in Table 3. Most participants taking antidepressants were on SSRIs (most commonly citalopram 132 [10·4%], sertraline 101 [8·0%], and paroxetine 36 [2·8%]), followed by atypical antidepressants (most commonly trazodone 106 [8·4%], bupropion 72 [5·7%], and mirtazapine 31 [2·4%]), TCAs (most commonly amitriptyline 50 [3·9%], nortriptyline 39 [3·1%]; and trimipramine 7 [0·6%]), and SNRIs (only venlafaxine 54 [3·2%], and duloxetine 31 [1·8%]). None of the participants were on any other class of antidepressant (e.g., MAOIs). Other psychoactive medications participants were taking were: sedatives (n=63, 5·0%; e.g., zolpidem, n=51, 4·0%), benzodiazepines (n=67, 5·3%; e.g., lorazepam n=63, 3·7%),

antipsychotics (n=25, 2.0%; e.g., quetiapine, n=22, 1.3%; generally as combination therapy), stimulants (n=5, 0.4%; e.g., modafinil n=5, 0.4%), and mood stabilizers (lithium n=3, 0.3%).

Participants were on their antidepressant for an average of 4.39 ± 3.19 years during the period of study, with an average of 71.1% of days covered. About half (46.6%) stopped taking their antidepressant during follow-up: 33/62 (53.2%) stopped taking SNRIs, 153/299 (51.2%) stopped taking SSRIs, 80/179 (44.7%) stopped taking atypicals, and 38/102 (37.3%) stopped taking TCAs during the period of study. Degree of adherence to any class of anti-depressants was not significantly associated with post-CR depressive symptoms (all $p > 0.05$).

Among the 220 participants with elevated PHQ-9 scores pre-CR, 202 (91.8%) were on any antidepressant medication, higher than among those without elevated scores (188/1046 [18.0%]; $p < 0.001$). Moreover, among participants on antidepressants, their mean pre-CR PHQ-9 scores were 7.33 ± 5.94 , and post-CR scores were 4.69 ± 4.87 (paired $t = 6.17$, $p < 0.001$; Figure 1). These scores were significantly higher than participants not on antidepressants both pre (4.98 ± 5.20 , $p < 0.001$) and post-CR (3.57 ± 4.43 , paired $t = 9.75$, $p < 0.001$). Participants taking any of the four classes of antidepressants experienced significant reductions in symptoms from pre-to post-program (all $p < 0.007$).

MACEs and their Associations with Depressive Symptoms and Antidepressant Use

Over a median follow-up of 4.7 ± 3.3 years, 264 (20.9%) participants had a MACE (Table 3).

Many participants had more than one MACE, and these participants had a mean of 2.36 ± 1.24

MACEs (median=2). Additionally, median time to total mortality for the 96 participants who died was 4.4 ± 3.0 years after CR initiation.

Greater pre-CR depressive symptoms were significantly associated with the occurrence of MACEs ($t=2.42$, $p<0.02$), specifically percutaneous coronary intervention ($t=2.86$, $p=0.04$), myocardial infarction ($t=2.42$, $p=0.02$), heart failure ($t=2.59$, $p=0.01$), and death ($t=2.88$, $p<0.01$). Moreover, the number of MACEs experienced by each participant was significantly associated with greater pre-CR depressive symptoms (Spearman's $\rho=0.06$, $p<0.02$). As shown in Table 3, use of antidepressants of any class was significantly associated with more MACEs (shown in the most common individual anti-depressants in supplemental table 1).

Propensity matching was successful in balancing participant characteristics among those taking antidepressant of a specific class versus those not (see supplemental tables 2-5). Cox regression models testing the association between a matched participant's use or non-use of each antidepressant class and the likelihood of MACE after CR are presented in Table 4. When considering different classes, the use of SSRIs, TCAs, and atypicals were associated with an increased risk of MACE, including death, while SNRIs were not. The Kaplan-Meier median survival rates were 67.2%, 60.0%, 68.6%, and 77.7% respectively ($p<0.01$). Kaplan-Meier curves displaying time to MACE by use of each antidepressant class are shown in Figure 2.

Given the different mechanisms of action and adverse effect profile of the individual antidepressants within classes, the most commonly-used medications (at least 50 patients) were tested individually in the same manner against matched controls. No difference in MACE risk

was observed for citalopram, trazodone, sertraline, bupropion, or venlafaxine (p -values >0.05), but was found for amitriptyline ($p=0.002$).

Proportion of days covered was significantly associated with occurrence of any MACEs, in those taking SSRIs ($74.6 \pm 11.9\%$ adherence in participants with any MACE vs $69.5 \pm 14.3\%$ adherence in participants having no MACEs, $p=0.02$), but not in those taking other antidepressant classes (all p -values >0.05). Proportion of days covered on any class was not significantly associated with death (all p -values >0.05).

Discussion

In this population-based cohort of CAD patients attending CR, it is shown that depressive symptoms are common. The high prevalence of depressive symptoms is consistent with what is reported in the literature.[5] A significant proportion of patients used antidepressants, which effectively lowered depressive symptoms, but was associated with higher incidence of MACEs.

In this study, one-third of CAD patients were on an antidepressant, which is higher than what has been previously reported.[32,33] In accordance with clinical recommendations for CAD patients with depression, most participants were on first-line recommended therapy, namely the SSRIs citalopram and sertraline, or second-line therapies, namely atypicals.[17] However, some patients were taking antidepressants which have not been well-studied in the CAD population (i.e., SNRIs) or that are not recommended in this population (i.e., TCAs).[34] Given that depression has been historically under-recognized and under-treated, the overall results herein

suggest symptoms are being detected and managed in accordance with the American Heart Association recommendations.[35]

This is one of the few studies in the literature to our knowledge to report on long-term antidepressant adherence and outcomes in a cardiac population, and the only one comparing antidepressant classes in CAD patients and their relationship with MACE, not just mortality. Up to one-half of participants stopped taking an antidepressant during the period of study, but whether discontinuation was due to side effects, remission, or another reason cannot be ascertained. Adherence to therapy [36] and discontinuation rates were consistent with what has been described in psychiatric samples more broadly.[34,37,38] Discontinuation rates were highest and proportion of days covered was lowest among those on SNRIs. Given the results herein suggest they may have a safer profile (see more below), tolerance of these medications (particularly of side effects such as insomnia and gastrointestinal issues),[39,40] warrant further study.

While antidepressant use was associated with reductions in depressive symptoms in the CR setting, use of all classes except SNRIs was associated with poorer cardiovascular outcomes. While SNRIs are considered as potential second-line therapy for CAD patients, they are understudied in this population.[17,34] While few patients were on SNRIs in the cohort and therefore lack of association could be due to low statistical power, the results did suggest fewer MACEs in patients taking SNRIs. Their safety profile was superior to the recommended first-line therapy of SSRIs. However, there are some reports of adverse cardiac effects in geriatric samples taking

venlafaxine XR, and therefore caution is warranted.[41] Unfortunately, we did not have this specific information regarding individual medications (e.g., long-acting) to confirm this.

MACEs were 1.5 times more common in those taking SSRIs or atypicals. Indeed, there has been some suggestion that SSRIs may not be as safe as previously described.[42–44] Some of the drugs in this class are associated with QT issues and can increase bleeding. However, some other research has shown SSRIs may be associated with lower re-hospitalization – an outcome we did not examine herein. These results suggest more research regarding individual SSRIs may be needed, given recommendations to prescribe them as first-line agents.[35]

Use of TCAs in the cohort was associated with 2.5 times higher rates of MACEs, as has been shown in psychiatric patients without CAD,[17,34] and in patients with CAD assessing mortality only.[42,45] To the best of our knowledge, this is the first study to show in a CAD population an increased rate of MACE with the use of TCAs, including fatal and non-fatal events. These results confirm recommendations not to prescribe TCAs in CAD populations. Appropriately, rates of use were low, consistent with previous research,[32,33] and may have been in patients who were taking those medications before the index event, or considered not to be in the early post-myocardial infarction or being at risk of long QT, or who suffered severe depression and were non-responsive to SSRIs. However, appropriateness cannot be ascertained with the available data.

No prior publication has directly compared the 4 major antidepressant classes and their rate of MACEs specifically in populations of CAD patients -- a comparison that will contribute to a

better understanding of current usage and safety of antidepressants in CAD patients. Results herein regarding poorer outcomes among CAD patients taking antidepressants are consistent with the limited literature in this area, which has been primarily in HF populations taking SSRIs, examined effects on mortality only, and not always adjusted for depression,[32,33,42,45,46] although results are not consistent with all literature.[34,47] In the Heart and Soul study for example, CAD patients broadly were included, and only 2 classes of antidepressants were considered (SSRIs and TCAs). TCAs (consistent with the findings herein) but not SSRIs were associated with increased mortality.[45] Rutledge et al. undertook a meta-analysis of the effects of mental health treatments (a composite of psychotherapy and antidepressants) on MACEs.[48] It was shown that treatment of depression, by either/both of these strategies, was associated with significantly *fewer* MACEs but no effect on total mortality. However, CR was associated with lower depression, MACEs and death. Finally, a recent meta-analysis including 11 studies of CAD patients showed no significant association of antidepressant use with mortality or MACEs, but findings did suggest that different classes of antidepressants had differential impact.[34]

The results of our study failing to show a lower rate of MACEs with use of antidepressant therapy adds to the wealth of evidence failing to prove that pharmacologic therapy of depression has any effect on MACE.[34,35] Because depression in CAD patients has consistently shown to be associated with increase rates of MACE, the apparent lack of benefit rendered by antidepressants calls for additional research to elucidate this paradox. Because certain classes of antidepressants are associated with increases in MACEs, it is plausible that the beneficial effect of some classes is being masked by the negative effect of other classes.[34] In future studies,

researchers should be certain not to report MACEs across antidepressant classes, but consider them separately.

Caution is warranted in interpreting the results. First, the design was observational, and hence causal associations between use of antidepressants and increased rates of MACEs cannot be drawn, in spite of the propensity matched analysis meant to reduce indication bias. Second, with regard to generalizability, our data are limited to a single center and to individuals with coronary artery disease attending CR, who were primarily male. However, the CR center was the only one available in the region, and therefore findings should be fairly representative of patients who attend CR in general. The generalizability of the cohort more broadly has been established elsewhere.[49]

Third, there was some retention bias in the sample, particularly that the analyzed cohort had higher depressive symptoms and greater use of antidepressants than those who did not complete the PHQ-9 at both time points and were hence excluded. Fourth, with regard to measurement, there was no structured clinical interview. Therefore, no definitive diagnosis of depression can be inferred from the data. Nor was there an assessment of depression that coincided with the time of antidepressant treatment initiation or follow-up appointments. Fifth, the effect of use of multiple antidepressants and dose were not considered. In addition, due to propensity matching and use of multiple antidepressants, a comparison between antidepressant classes could not be performed. Finally, while all CR participants were exposed to stress management, the use of psychotherapy, which is another evidence-based treatment for depression, was not ascertained in this group and therefore could not be considered in the analyses.

In conclusion, depressive symptoms and use of antidepressants are common in CR. Use of antidepressants is generally in accordance with clinical practice guideline recommendations. Use of antidepressants was associated with lower depressive symptoms, but often more adverse cardiac events. The safety profile of SNRIs warrants further consideration.

Declaration of Interests

All authors declare no financial or personal interests.

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