Hormone Therapy Use in Women Veterans Accessing Veterans Health Administration Care: A National Cross-Sectional Study

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ABSTRACT: The majority of women Veterans using VA (Veterans Administration) care fall in the 45–65 year-old age range. Understanding how menopause is managed in this group is of importance to optimizing their health.

OBJECTIVE: National population estimates showed a prevalence of hormone therapy (HT) use by women over 45 years of 4.7 % (2009–2010). Our study described the frequency of HT use among women Veterans in VA, and examined whether mental health (MH) was predictive of HT use.

DESIGN: This was a cross-sectional analysis of national VA administrative data for fiscal year 2009.

PARTICIPANTS: Women Veterans over the age of 45 (N=157,195) accessing VA outpatient care were included in the analysis.

MAIN MEASURES: Logistic regression analyses using HT use as the dependent variable.

KEY RESULTS: Mean age was 59.4 years (SD =12.2, range =46–110), and 16,227 (10.3 %) of all women used HT. Hysterectomy (OR 3.99 [3.53, 4.49]) and osteoporosis (1.34 [1.27, 1.42]) were the strongest medical indicators of HT use. A total of 49,557 (31.5 %) women in the sample received at least one primary diagnosis of a MH disorder and were more likely to use HT than women with no MH diagnoses (unadjusted OR 1.56, 95 % CI [1.50, 1.61]). Women Veterans with a mood disorder (depression/bipolar) or anxiety disorder [post-traumatic stress disorder (PTSD), other anxiety diagnoses] were more likely to use HT after controlling for demographics and medical comorbidity.

CONCLUSION: The prevalence of HT use among women Veterans using VA is more than twice that of the general population. Prior work suggested that women Veterans were discontinuing HT at comparable rates, but these data demonstrate that decline in VA HT use has not kept pace with that of civilian medical care. The association of MH diagnosis with HT use suggests that MH plays an important role in VA rates. Further study is needed to understand contributing patient and provider factors.

Received April 6, 2014
Revised September 19, 2014
Accepted October 15, 2014
Published online November 6, 2014

KEY WORDS: women Veterans; hormone therapy; mental health.
J Gen Intern Med 30(2):169–75
DOI: 10.1007/s11606-014-3073-9

BACKGROUND

Hormone therapy (HT) with estrogen-progestin combinations (EPT) or, after hysterectomy, with estrogen alone (ET) has been used since the 1940s to treat menopausal symptoms and prevent chronic disease. The early termination of the Women's Health Initiative (WHI) (2002),[1] due to the unexpected finding of increased cardiac risk with EPT, resulted in a dramatic decline in HT use. Immediately following WHI publication, HT usage declined by 50–70 %.[2] More recent national estimates continued to show declining HT use among women over 45 years of age, from 22.4 % in 1999–2000 to 4.7 % by 2009–2010.[3]

Although estrogen use is no longer recommended for chronic disease prevention,[4,5] consensus guidelines advise that systemic HT is a reasonable option for women (up to age 59 or within 10 years of menopause) who have difficulty tolerating moderate to severe menopausal symptoms, including vasomotor symptoms (VMS) and vaginal dryness.[6] EPT is recommended for short-term use (5 years) in women ages 50–59.[4] While use of ET has been considered acceptable for longer use,[4] accumulating evidence suggests that health risks increase with time.[6–9]

Some women elect to remain on HT beyond recommended time frames, despite evidence supporting limited use.[10] Studies examining HT decision-making conducted after WHI publication suggest that as many as 44 % of women attempting to discontinue HT resume it due to VMS.[11,12] Mood and sleep disturbances were also associated with unsuccessful HT discontinuation.[13]

Since the menopausal transition is often stressful due to its marked physiologic changes, research has focused on the association between estrogen and mood.[14,15] While some

population-based work has found an association between HT use and mental health (MH) conditions,[16] data is lacking from clinical settings treating menopausal women with chronic pre-existing MH conditions.

As women enter the military at unprecedented rates, the number of women Veterans (WV) enrolling in Veterans Health Administration (VA) care has grown dramatically.[17] The majority of women using VA are in midlife; in fiscal year (FY) 2010, women ages 45–64 were the largest group of female users.[17] Since the majority of WV accessingVA now fall in the menopausal age range,[17] understanding their HT use is critical.

Shortly after the WHI, WV discontinued HT at rates similar to the general population (e.g., 66–77 %).[2,18,19] In a national VA administrative data study of HT use before and after WHI publication,[19] patients with histories of breast cancer or coronary artery disease, as well as older and Hispanic WV were more likely to have discontinued HT. Conversely, those with depression, post-traumatic stress disorder (PTSD) or alcohol use disorders were significantly less likely to have discontinued HT. A second VA study that surveyed WV regarding HT discontinuation found that severity of menopausal symptoms after HT use and longer duration of prior HT use predicted resumption.[18] No studies of HT have been conducted in the VA since 2004, and the population of midlife WVs has grown substantially since then.[17] In addition, no VA research has compared users and nonusers of HT.

Since WV using VA are known to have a high prevalence of trauma exposure and MH disorders,[20] and estrogen appears to act as a mood regulator,[14,21] it is conceivable that those who take HT may experience a reduction in mood symptoms. Also, given the prior findings that WV with PTSD were more likely to continue HT shortly after WHI,[19] it is conceivable that women with trauma histories perceive VMS as similar to hyperarousal symptoms characteristic of PTSD and other mood and anxiety disorders. These women may have greater difficulty tolerating these symptoms and/or perceive more benefit from their reduction.

Objectives/Hypotheses of the Current Study

The current study had two primary aims: 1) to determine the frequency of HT use among WV in the VA during FY 2009 (and compare it to use among civilian women nationally), and 2) to ascertain whether documented MH conditions were associated with HT use in VA. Our hypotheses were: a) VA frequency of HT use exceeds comparable reports of use outside the VA, and b) WV with MH conditions are more likely to use HT than those without these diagnoses.

METHODS

This study examined a national sample of female VA users. Inclusion criteria were: Veteran status, at least one VA outpatient visit in FY 2009, and age greater than 45 years. Transgender Veterans (n=290) were excluded. The Institutional Review Boards of VA Boston and VA Connecticut Healthcare Systems approved the study.

FY 2009 patient specific data were extracted from VA administrative files in the National Patient Care Database (NPCD). HT users were identified through the Pharmacy Benefits Management Program (PBM), a centralized, electronic system that tracks all medication ordered in the VA. HT was defined as receipt or listed use of any oral or transdermal estrogen-containing product or combined estrogen/progestin product not used for contraceptive purposes during FY 2009.

Data from the PBM were then linked to the NPCD Outpatient Clinic Files and Inpatient Patient Treatment Files located at the Austin Automation Center, TX; these databases provide demographic and clinical information on all patients in VA.

NPCD files code race and ethnicity separately. To construct a consolidated race variable, we first categorized the given race descriptions as White, Black, or Other. A fourth category, Hispanic, was created by recoding women with Hispanic ethnicity, regardless of given race. Race descriptions of Unknown or Declined to Answer were coded as missing (28 % of the sample). For subsequent analyses, these missing values were filled in using a single imputation method based on random forest recursive partitioning.[22]

The ICD-9-CM codes associated with specific VA inpatient and outpatient visits were used to categorize the following exposure and confounder variables: mental health diagnoses included PTSD, depression, bipolar disorder, anxiety and psychotic disorders, both alcohol and drug abuse and dependence, somatization, and eating disorders. The medical diagnoses included hysterectomy, osteoporosis, hypertension, diabetes, breast and endometrial cancers, obesity, congestive heart failure, coronary artery disease, peripheral vascular disease, cerebrovascular disease, venous thromboembolism, liver disease and dementia. Because of this study's focus on the relationship between MH diagnoses and HT use, we attempted to be inclusive in selecting MH variables. In contrast, because the medical diagnoses were conceptualized as potential confounders of HT use, we were more strategic in selecting medical diagnoses for which HT use was either potentially beneficial or contraindicated.[4,23–25].

Statistical Analyses

First, the frequency of HT use was calculated for all WV in FY 2009. We next determined whether the presence of MH disorders [as indicated by a corresponding International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis] predicted HT use. HT users and nonusers were compared on demographics and MH diagnoses, and unadjusted odds ratios were calculated for these variables. We created a dichotomous variable for presence or absence of MH diagnosis. Secondly, logistic regression was used to

calculate the adjusted odds ratios associated with presence of a MH disorder after accounting for demographic characteristics and medical comorbidities with known associations. All analyses were conducted using the R statistical programming software (version 3.0.1, R Core Team, Vienna Austria).

Logistic Regression (LR) Model of HT Use

The full LR model of HT use was constructed by entering sets of predictors in sequence, in order to assess the incremental predictive ability of each set. The first set included four demographic characteristics: age, race, marital status, and smoking status. We created a five-level categorical variable for age, to facilitate the comparison of interest (i.e., older vs. younger women).

The goal of the next set was to control for medical conditions potentially associated with HT use. To find a parsimonious set, the pre-selected medical diagnosis variables competed for entry into the model containing all demographic predictors. Over a series of steps, predictors were chosen for entry (or removal if already entered) based on the choice that carried the largest possible improvement in penalized model-data fit (i.e., Bayes Information Criterion, BIC). The steps halted when fit could no longer be improved by additions or removals. This sequence was repeated in each of 50 bootstrap samples; only predictors chosen in all samples were included in the final set.

The final set of predictors (Set 3) comprised the MH diagnoses. Again, the goal was to identify only those diagnoses that improved on the prediction of HT use above and beyond the demographics and medical comorbidities. As such, MH variables competed for entry into a model containing all demographic predictors and the medical diagnoses selected in the previous set, using the same stepwise procedure described above.

RESULTS

A total of 157,195 WV met criteria for inclusion in the study. Mean age for the complete sample was 59.4 years (SD = 12.2, range = 46–110). The PBM data indicated that 16,227 (10.3 %) of all women over 45 years of age seen in the VA in 2009 used HT. Tables 1 and 2 compare HT users to non-users on demographic characteristics and medical diagnoses. HT use was most prevalent among women who were 50–59 years old, White, married or divorced, and never smokers.tgrouptgroup

Hysterectomy and osteoporosis were the strongest medical indicators of HT use. In separate analyses (available on request), in all age groups, women with a hysterectomy were more likely to be using HT. The association was strongest in the youngest age group, but then fairly consistent across older groups. Similarly, for osteoporosis, it was primarily the youngest women with osteoporosis who were most likely to be prescribed HT. Among older groups, there was only a slightly elevated likelihood.

A total of 49,557 (31.5 %) women in the sample received at least one primary diagnosis for a MH disorder of interest (Table 3). Of these, 13.3 % (n=6,580) used HT in the same year, and they represented 41 % of all HT users identified. Women with at least one MH diagnosis were more likely to use HT than women with no MH diagnoses (unadjusted OR 1.56, 95 % CI [1.50, 1.61]). Table 3 provides prevalence estimates for individual MH diagnosis categories by HT use and corresponding unadjusted odds ratios. All MH diagnoses were associated with greater odds of HT use, with the exception of psychotic , and substance/alcohol use disorders.tgroup

Table 4 summarizes the results from the LR model. The five demographic predictors—age, race, marital status, and smoking status—entered the model as Set 1. All predictors were statistically significant.tgroup

The 14 medical diagnoses (Table 2) competed for entry to the model as part of Set 2. Table 4 shows the five selected medical diagnoses and their corresponding adjusted odds ratios; the addition of this set resulted in a significant improvement in model-data fit over demographics alone, χ^2 (5) = 957, p<0.001.

After the nine MH diagnostic category predictors competed for entry to the model as part of Set 3, the final model indicated that WV with a mood disorder (depression or bipolar) or an anxiety disorder (PTSD or other anxiety disorders) are more likely to use HT, controlling for demographics and medical comorbidity. The addition of MH diagnoses (Set 3) resulted in a significant improvement in model-data fit over demographics and medical diagnoses, χ^2 (6) = 580, p<0.001.

DISCUSSION

The 10.3 % prevalence of HT use among WV using VA is more than twice the prevalence in the general population (4.7 %).[3] Because long-term HT may confer risk for disease, it is critical to understand this difference. While prior work suggested that WV were discontinuing HT at rates comparable to those outside VA,[2] these more recent data demonstrate higher rates of HT use in the VA than those reported in the general US population.

As hypothesized, WV VA users with MH diagnoses were more likely to use HT. To illustrate the magnitude of this relationship, the presence of any MH diagnosis exhibited odds comparable to osteoporosis, a condition for which HT is still considered appropriate as second-line treatment.[4,25] Increased rates of MH comorbidity in WV[26] may partially explain the observed higher prevalence of HT use. The poorer MH of WV VA users as compared to women in the general population[20] may contribute to continuation of HT use through multiple mechanisms. From a physiologic standpoint, low estrogen

Table 1. Demographics and Unadjusted Odds Ratios for HT Use

	Non-users (n = 140,968)	HT users (n = 16,227)	
Characteristic	No. (%)	No. (%)	OR [95 % CI]
Age category			
<50	29,999 (21)	2,679 (17)	1 [Reference]
50–59	60,013 (43)	8,525 (52)	1.59 [1.52, 1.67]
60–69	22,422 (16)	3,148 (19)	1.57 [1.49, 1.66]
70–79	11,646 (8)	1,031 (6)	0.99 [0.92, 1.07]
≥80	16,888 (12)	844 (5)	0.56 [0.52, 0.61]
Race			
White	84,985 (60)	10,893 (67)	1 [Reference]
Black	36,436 (26)	3,473 (21)	0.74 [0.71, 0.77]
Hispanic	8,940 (6)	904 (6)	0.79 [0.73, 0.85]
Other	10,607 (8)	957 (6)	0.70 [0.66, 0.75]
Marital status			
Never married	28,327 (20)	2,524 (15)	1 [Reference]
Married	47,220 (33)	6,272 (39)	1.49 [1.42, 1.56]
Divorced	47,743 (34)	6,132 (38)	1.44 [1.37, 1.51]
Separated or widowed	17,678 (13)	1,299 (8)	0.82 [0.77, 0.88]
Smoking status			
Never smoked	63,904 (45)	7,629 (47)	1 [Reference]
Current smoker	50,675 (36)	5,582 (34)	0.92 [0.89, 0.96]
Past smoker	26,389 (19)	3,016 (19)	0.96 [0.92, 1.00]

HT hormone therapy, OR unadjusted odds ratio of HT use (compared to reference category), CI confidence interval

appears to impact extinction of conditioned fear responses and retention of extinction learning.[27,28] Thus, women with relatively low estrogen levels may have difficulty learning that previously conditioned stimuli are no longer signaling an aversive event. These findings suggest that low estrogen may be a vulnerability factor for developing and maintaining PTSD after traumatic events.[27,29] Separately, estrogen positively impacts serotonin receptor distribution, implicating it as a mood regulator[30] that could promote HT continuation, particularly by women with mental illness.[31] Mechanisms such as these may make it difficult for vulnerable women to discontinue HT without experiencing significant psychological distress.

Additionally, sustained HT use in WV with MH conditions may be related to their experience of VMS. Anxiety is the most common psychological symptom associated with VMS[32,33]; both negative affect and degree of postmenopausal anxiety are linked to higher reporting of bothersome VMS.[33,34] WV with mental health comorbidity may experience enhanced somatic amplification, which is known to increase symptom perception and problem reporting from VMS.[35]

Interpersonal trauma, also a common exposure among WV,[20] may also contribute to the higher prevalence of HT use. In a large longitudinal study, child abuse was linked to increased VMS reporting among midlife women.[36] WV are more likely to have experienced childhood abuse[37] as well as other interpersonal trauma before, during and after military service.[20] Trauma impacts subsequent physical symptoms and poor health outcomes through physiologic alterations in the hypothalamic-pituitary-adrenocortical (HPA) axis.[38] Estrogen enhances HPA activity,[21] perhaps suggesting a causal

Table 2. Prevalence of Medical Diagnoses and Unadjusted Odds Ratios for HT Use

	Non-users (*n* = 140,968)	HT users (*n* = 16,227)	
Medical Diagnosis	No. (%)	No. (%)	OR [95 % CI]
Hysterectomy	870 (0.6)	392 (2)	3.99 [3.53, 4.49]
Hypertension	46,022 (33)	5,834 (36)	1.16 [1.12, 1.20]
Peripheral vascular disease	1,687 (1)	178 (1)	0.92 [0.78, 1.07]
Coronary artery disease	5,967 (4)	573 (4)	0.83 [0.76, 0.90]
Congestive heart failure	2,156 (2)	167 (1)	0.67 [0.57, 0.78]
Osteoporosis	10,960 (8)	1,649 (10)	1.34 [1.27, 1.42]
Obesity	15,216 (11)	1,900 (12)	1.10 [1.04, 1.15]
Breast cancer	3,114 (2)	112 (0.7)	0.31 [0.25, 0.37]
Endometrial cancer	158 (0.1)	15 (0.1)	0.82 [0.47, 1.35]
Venous thromboembolism	27 (< 0.1)	2 (< 0.1)	0.64 [0.10, 2.15]
Cerebrovascular accident	2,723 (2)	257 (2)	0.82 [0.72, 0.93]
Diabetes	20,001 (14)	2053 (13)	0.88 [0.83, 0.92]
Dementia	422 (0.3)	17 (0.1)	0.35 [0.21, 0.55]
Liver disease	726 (0.5)	112 (0.7)	1.34 [1.09, 1.63]

HT hormone therapy, OR unadjusted odds ratio of HT use (diagnosis present vs. diagnosis absent), CI confidence interval

Table 3. Prevalence of Mental Health Diagnoses and Unadjusted Associations with HT Use

	Non-users (n = 140,968)	HT users (n = 16,227)	
MH Diagnosis	No. (%)	No. (%)	OR [95 % CI]
Any MH diagnosis	42,977 (30)	6,580 (41)	1.56 [1.50, 1.61]
Alcohol use disorders	3,946 (3)	452 (3)	0.99 [0.90, 1.10]
Drug use disorders	2,670 (2)	333 (2)	1.09 [0.97, 1.22]
Psychotic disorders	6,920 (5)	678 (4)	0.84 [0.78, 0.91]
Bipolar disorders	7,299 (5)	1,233 (8)	1.51 [1.41, 1.60]
Depressive disorders	27,666 (20)	4,662 (29)	1.65 [1.59, 1.71]
PTSD	11,641 (8)	2,089 (13)	1.64 [1.56, 1.72]
Other anxiety disorders	9,361 (7)	1,613 (10)	1.55 [1.47, 1.64]
Somatization disorders	235 (0.2)	49 (0.3)	1.81 [1.32, 2.44]
Eating disorders	218 (0.1)	38 (0.2)	1.52 [1.06, 2.11]

HT hormone therapy, OR unadjusted odds ratio of HT use (diagnosis present vs. diagnosis absent), CI confidence interval

relationship between trauma and VMS. To our knowledge, there are no published studies specifically investigating adult interpersonal trauma and VMS; however, substantial literature exists on adult trauma exposure and increased physical symptom reporting.[39–41] Unfortunately, there was no measure of childhood, or other trauma exposure included in these data.

While mental health comorbidity is an important correlate of HT use in WV, we found that hysterectomy was the strongest overall predictor of HT use. Prior work has demonstrated increased rates of hysterectomy among WV, in the VA[42] and in population-based samples.[26] Since chronic pain pelvic pain is sometimes an indication for hysterectomy,[43] and is associated with both sexual assault and mental health conditions,[44] it is conceivable that WV with trauma histories and comorbid mental illness may be more likely to undergo hysterectomy, which in turn could have contributed to the increased frequency of HT use seen in these data. Supplemental analyses (available upon request), however, demonstrated that hysterectomy is a strong predictor of HT independent of MH diagnosis.

Finally, another possible explanation for the observed elevated frequency of HT in this study is patient–provider decision making factors not measurable in our data. For example, perhaps WV, who began HT during peri-menopause, did not subsequently stop it as they entered post-menopause with its more stable estrogen levels. Provider input has been an important correlate of initiation/discontinuation of HT in prior work.[13] VA providers may not have appropriately counseled women on the risks/benefits of HT (taking into account timing or duration of use), or may have been less likely to discontinue HT in women with mental illness. There remain many unmeasured factors relevant to understanding the observed elevated frequency of HT use in VA.

Our findings have a number of limitations. These data are cross-sectional; therefore, causality, timing (age of onset of use) and total exposure to HT cannot be evaluated. This study also could not measure patient adherence to HT, and extracted diagnoses may not accurately reflect true clinical diagnoses. We lacked data identifying WV who received HT prescriptions outside the VA, potentially misclassifying some WV. Veterans accessing care outside the VA often have lower disability ratings,[45] potentially introducing bias by excluding healthier, less disabled women from these data. Body Mass Index (BMI) has been associated with VMS[46]; however, this data set only contains diagnosis code data on obesity. In our analyses, obesity had an unadjusted association with HT;

Table 4. Multivariable Logistic Regression Models Predicting Use of Postmenopausal Hormonal Therapy by Women Veterans

Predictor	AOR [95 % CI]
Set 1	
Age category	
< 50	1 [Reference]
50–59	1.52 [1.45, 1.59]
60–69	1.36 [1.28, 1.44]
70–79	0.83 [0.77, 0.90]
≥ 80	0.46 [0.42, 0.50]
Race	
White	1 [Reference]
Black	0.66 [0.64, 0.69]
Hispanic	0.65 [0.61, 0.70]
Other	0.57 [0.53, 0.61]
Marital status	
Never married	1 [Reference]
Married	1.43 [1.36, 1.51]
Divorced	1.36 [1.29, 1.43]
Separated or widowed	1.08 [1.00, 1.17]
Smoking status	
Never smoked	1 [Reference]
Current smoker	0.81 [0.78, 0.84]
Past smoker	0.93 [0.89, 0.97]
Set 2*	
Hysterectomy	3.72 [3.29, 4.21]
Osteoporosis	1.36 [1.29, 1.44]
Hypertension	1.27 [1.22, 1.32]
Diabetes	0.78 [0.74, 0.82]
Breast cancer	0.27 [0.23, 0.33]
Set 3**	
Depressive disorders	1.39 [1.33, 1.45]
Bipolar disorders	1.30 [1.21, 1.38]
PTSD	1.27 [1.20, 1.34]
Other anxiety disorders	1.14 [1.07, 1.21]
Psychotic disorders	0.83 [0.76, 0.90]
Alcohol use disorders	0.77 [0.69, 0.85]

HT hormone therapy, AOR odds ratio of HT use (diagnosis present vs. diagnosis absent) adjusted for previously and concurrently entered predictors, CI confidence interval

**Set 2: chronic condition models also control for the demographic Set 1 variables*

***Set 3: controls for all of the preceding variables*

however, this effect disappeared when controlling for other confounders in the adjusted LR model. Nonetheless, these administrative data likely underestimate the true prevalence of elevated BMI in this WV cohort. Finally, hysterectomy rates are likely underestimated, as WV may undergo the surgery outside VA. The rates of obesity and hysterectomy in this study are both lower than previously published VA rates utilizing other study designs.[42,47]

Additional work is needed to understand the high frequency of HT use in the VA compared to that of the general population. Prospective, longitudinal studies will better inform our understanding of WV HT use over time. Mixed methods designs examining VA patients' experience of VMS, as well as decision- making around HT use and discontinuation, could be key to explaining the elevated rates found in this study.

Finally, ascertainment of providers' knowledge and prescribing patterns will also yield key information. Alternative, strategies for managing VMS and other symptoms tailored for women with chronic MH conditions are worthy of explanation. Finally, development of Veteran-informed interventions or implementation of decision aids to improve both symptom management and prescribing practices could be a promising contribution.

CONCLUSION

The decision to continue or stop HT is complex, and complicated by changing information and guidelines. As with all pharmacologic therapies, individual risks and benefits must always be evaluated before making treatment decisions. The finding that MH conditions were strongly associated with HT use among WV suggests the need for further study of both patient-specific factors and patient/provider decision-making around HT in this unique and growing population of patients.

Acknowledgements: *The authors wish to acknowledge the assistance of Melissa Skanderson, MSW.*

Funding to support database creation was provided by National Center for PTSD (NCPTSD), U.S. Department of Veterans Affairs, Executive Division, White River Junction, VT.

This work was supported in part by Career Development Award (Japuntich) #1IK2CX000918-01A1from the United States Department of Veterans Affairs Clinical Sciences Research and Development Service.

This study was presented in abstract form at the Society for General Internal Medicine (SGIM), 36th Annual Meeting, April 26, 2013, Denver, CO.

The contents of this manuscript do not represent the views of the Department of Veterans Affairs or the United States Government.

Conflict of Interest: *The authors declare that they do not have a conflict of interest.*

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