Effects of Positive Airway Pressure Treatment on Clinical Measures of Hypertension and Type 2 Diabetes

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Purpose: Mechanistic and observational studies support an independent increase in risk of hypertension and abnormal glucose metabolism associated with obstructive sleep apnea (OSA). However, the specific populations and outcomes that improve with treatment of OSA in clinical practice are not established. We examined the effectiveness of OSA treatment on clinical blood pressure and diabetes control measures in men with preexisting systemic hypertension or type 2 diabetes.

Methods: A retrospective cohort of veterans (n = 221) with a new diagnosis of OSA and initiation of positive airway pressure treatment was identified using administrative databases and clinical records.

Measurements and Results: Outcomes were changes in blood pressure (BP; mean of 3 highest recordings; systolic and diastolic) and glycemic control (mean of 3 highest fasting glucose and hemoglobin A1C values) at 3-6 months (T1) and 9-12 months (T2) following treatment compared to pretreatment. A generalized estimating equation model was used with adjustment for potential confounders: demographics, body mass index (BMI), OSA severity, Charlson comorbidity index, and pharmacologic treatment for hypertension and diabetes. Sustained independent effects of OSA treatment (mean change [95% CI]) were noted in both systolic BP (T1: [-7.44 [-10.41 to -4.47] and T2: [-6.81 [-9.94 to -3.67]]) and diastolic BP (T1: [-3.14 [-4.99 to -1.29] and T2: [-3.69 [-5.53 to -1.85]]). Diabetes control measures did not change with OSA treatment.

Conclusions: Treatment of OSA improves office blood pressure in hypertensive men. Prospective studies are necessary to better characterize specific populations with OSA that benefit from treatment with respect to progression of hypertension and type 2 diabetes.

Keywords: Effectiveness, OSA, hypertension

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Considerable evidence from observational studies implicates obstructive sleep apnea (OSA) as an independent risk factor for systemic hypertension1 and abnormal glucose metabolism.2 The results of experimental studies evaluating effects of OSA treatment in hypertension reveal modest benefits,3,4 and the data regarding improvement in glucose homeostasis in type 2 diabetes from small clinical trials are inconsistent.5,6 This discrepancy is partly due to the size and type of cohorts examined or the specific outcomes assessed.7 Several studies examined populations with differential baseline characteristics (presence or absence of preexisting hypertension/diabetes) or variable OSA disease severity.7,12 Additional sources of variability relate to duration of follow-up and levels of treatment adherence.13 However, frequently the outcomes examined are not routinely available in clinical practice, and the applicability of these findings to usual care settings is unclear.

The objective of this study was to examine the effectiveness of treatment of OSA on routine clinical measures of hypertension and diabetes control in a primary care practice setting. We examined the long-term effects of OSA treatment on diurnal office BP, fasting glucose, and hemoglobin A1C (HbA1C) in veterans with newly diagnosed OSA and comorbid systemic hypertension and/or type 2 diabetes.
identified by ICD9 codes. New diagnosis of OSA with initia-
tion of treatment was defined as: (1) a CPT code for a di-
nostic sleep procedure (polysomnography; PSG or unattended
level 3 portable monitoring, Stardust II, Philips-Respironics;
PM) followed by an ICD-9 code for OSA within 3 months; (2)
prosthetics records indicating CPAP or APAP device provision
within 6 weeks of the diagnostic procedure; (3) no OSA ICD-9
code in administrative and clinical records for 6 months prior
to the diagnostic procedure date. The exclusion criterion was CPT
codes for or history of surgical or dental device treatment for
OSA. Subjects received either laboratory titrated fixed-CPAP
treatment (Remstar Pro, Philips-Respironics, Inc; Murrysville,
PA, USA) or APAP device treatment set at 4 to 20 cm H₂O upon
initiation (Remstar Auto with C-Flex, Philips-Respironics). The
veterans with both fixed CPAP and APAP treatments had simi-
lar outpatient follow-up with sleep medicine physicians, and
the APAP device pressure was adjusted to ≥ 90 percent after
administration of medications for treatment of hypertension and diabetes. Three
pharmacologic treatment measures were considered as covari-
ates: changes in number of drugs, changes in dose of drugs,
and adherence to drugs. Adherence to medications for hyper-
tension and diabetes was defined by the medication possession
ratio (MPR).\textsuperscript{16} MPR calculations results in a ratio < 1.0 if there
are lapses in prescription refilling. The MPR was truncated at
the maximum value of 1.0 (indicating potentially perfect adher-
ence). An MPR was calculated for each 90-day interval (T1 and
T2) and for each drug. The mean MPR for each drug class (an-
thypertensive and oral plus injectable hypoglycemics) within
T1 and T2 individually were used as a measure of adherence
to pharmacologic treatment. Total number of antihypertensive
and antihyperglycemic medications as well as dose changes
was recorded. Change in total number of medications during
each follow up interval compared to baseline was coded as -3
to +3 (0 being no change in number of medications). Change
of medications within the same class (e.g., ACE inhibitors) and
replacement of one drug with another was not considered. Dose
changes of individual medications was recorded categorically: none (0), increase (+1), and decrease (-1).

**Figure 1—Cohort Identification**

<table>
<thead>
<tr>
<th>Subjects with OSA diagnostic procedure codes: National Patient Care Databases (NPCD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 1,401 (VAMC1 = 1,075; VAMC2 = 326)</td>
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<table>
<thead>
<tr>
<th>Subjects with new diagnosis of OSA and with Systemic Hypertension and/or Type 2 diabetes (NPCD)</th>
</tr>
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<tbody>
<tr>
<td>N = 650 (VAMC1 = 490; VAMC2 = 160)</td>
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</table>

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<tr>
<th>Subjects with initial issue of a Device from National Prosthetics Patient Database (NPPD)</th>
</tr>
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<tr>
<td>N = 302 (VAMC1 = 219; VAMC2 = 83)</td>
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<tr>
<th>Subjects remaining after clinical records review for exclusion criteria</th>
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<td>N = 221 (VAMC1 = 149; VAMC2 = 72, 220 males)</td>
</tr>
</tbody>
</table>

Analysis

The index date for the study was the date of CPAP or APAP
device distribution. Three months preceding the index date
was defined as the baseline period (T0), 3-6 months following the
index date as T1 (first follow-up), and 9-12 months following the
index date as T2 (second follow-up). The outcomes
assessed (final cohort, n = 221) at T1 and T2 were: (1) Outpatient
office visit systolic and diastolic BP (from the same recordings)
in the subjects diagnosed with hypertension. For conservative
treatment-related effect estimates, an average of the highest
3 values was taken to represent the systolic and diastolic BP
within each time interval. (2) Outpatient fasting glucose values
extracted from clinical records. If multiple values were noted,
the last value within each time interval (T0, T1, and T2) was
recorded. If the lab did not specifically indicate fasting glucose
in the remarks, an outpatient blood draw that occurred between
07:00 to 08:30 was considered a fasting sample. (3) Outpatient
hemoglobin A1C (HbA1C) extracted from clinical records. If
multiple values were noted, the last value within each time in-
terval (T0, T1, and T2) was recorded.

Several potential confounders were assessed, including: de-
ographic data (age, race, BMI), concurrent medical illnesses
per ICD9 codes, drug treatment of hypertension and diabetes,
objective OSA treatment adherence (SmartCard download to
EncorePro software), and self-reported daytime sleepiness doc-
umented in clinician notes. Demographic, comorbid medical
disorders, and pharmacy data were extracted from administra-
tive records. Data regarding vital signs, OSA disease severity,
OSA treatment adherence, and symptom of sleepiness were
extracted from clinical records. OSA disease severity was de-
defined by the apnea hypopnea index (AHI) per published criteria
for PSG.\textsuperscript{14} For both PSG and PM, the criterion for hypopnea
was ≥ 50% airflow reduction and ≥ 3% desaturation (or associ-
ated arousal for PSG). The Charlson comorbidity index (CCI)
was calculated and used to indicate general health status.\textsuperscript{15}
The pharmacy data provided the total number and dosage of medi-
cations used for treatment of hypertension and diabetes. Three
pharmacologic treatment measures were considered as covari-
ates: changes in number of drugs, changes in dose of drugs,
and adherence to drugs. Adherence to medications for hyper-
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of medications within the same class (e.g., ACE inhibitors) and
replacement of one drug with another was not considered. Dose
changes of individual medications was recorded categorically: none (0), increase (+1), and decrease (-1).

**Statistical Analysis**

Comparisons of sociodemographic characters of the final co-
hort to those lost to follow-up (Figure 1) were performed with χ²
or t-tests. Primary outcomes were examined for treatment-
related changes in outcomes at T1 and T2 using the generalized
estimating equation (GEE) model, where the final model was
adjusted for time and the potential covariates described above.
OSA disease severity was treated as a categorical variable with
2 levels: mild (AHI or RDI 5-15) and moderate to severe (AHI
or RDI > 15). Daytime sleepiness symptom was coded as a cat-
egorical variable (yes/no/missing). Multicollinearity amongst
the covariates was checked with variance inflation factor (VIF, < 5 accepted). In the stratified analyses (by type of treatment; CPAP vs. APAP and by race; European Americans vs. African Americans), similar adjusted GEE model was used with added variables of groups as defined above and time-group interaction terms. Adherence to OSA device treatment (CPAP or APAP) was treated as a continuous variable (average nightly use in hours and minutes). Due to significant missing data, adherence to OSA treatment was excluded as a covariate in the final GEE model. The effect of adherence to OSA treatment on individual outcomes was separately examined with general linear regression. All analyses were performed using SAS 9.2, and a p-value ≤ 0.05 was considered significant.

RESULTS

Cohort Lost to Follow-Up (Figure 1)

As total of 650 veterans were diagnosed with OSA, but only 302 were identified as receiving treatment (CPAP or APAP device) within 6 weeks of diagnosis. Veterans who did vs. did not receive treatment were not different by race (p = 0.81), marital status (p = 0.54), or age (p = 0.57).

Baseline Measurements (Table 1)

Ninety-four percent of participants had a diagnosis of hypertension, while 40% had type 2 diabetes. Approximately one-fourth had mild sleep apnea, and more than half reported no daytime sleepiness. A third of the subjects were treated with APAP long-term in the autoadjusting mode. Compared to those treated with CPAP, the APAP treated subjects had higher BMI (33.9 ± 6.3 vs. 35.9 ± 5.7, p = 0.02) and were more frequently ethnic minorities (28% vs. 68%, p < 0.0001). The preponderance of African Americans veterans among those treated with APAP reflects the practice patterns at the 2 study sites (i.e., the urban VAMC utilizes APAP more frequently). Due to this difference in treatment modality with regards to race, we examined the effect of race on baseline characteristics of the cohort. African Americans (AA) compared to European Americans (EA) and Hispanics/other were not different in OSA disease severity, self-reported sleepiness, or the prevalence of hypertension or diabetes at baseline. However, AA veterans were younger (59.5 ± 10.9 vs. 64.7 ± 10.5, p = 0.007), more obese (BMI 36.5 ± 5.9 vs. 33.9 ± 6.3, p = 0.004), and had lower adherence to pharmacologic treatment (MPR) for hypertension (0.96 ± 0.09 vs. 0.98 ± 0.03, p = 0.01) and diabetes (0.93 ± 0.13 vs. 0.97 ± 0.05, p = 0.05).

Effects of OSA Treatment (Table 2): Primary Outcomes

Both systolic and diastolic BP decreased significantly with initiation of OSA treatment at both T1 and T2. No significant change in fasting glucose or HbA1C was noted at either T1 or T2 after initiation of PAP treatment. Of the other factors (explanatory variables) considered in the model, age was significant with regard to BP outcomes. Specifically, increasing age was associated with a greater reduction in both systolic BP (p = 0.04) and diastolic BP (p < 0.0001). A second significant factor was change in dose of antihypertensive medications. An increase in dose of antihypertensive medications was related to less reduction in diastolic BP (p = 0.03; systolic not significant at p = 0.08), likely reflecting a response rather than a causal effect.

For glucose control measures, OSA treatment had no independent effect on fasting glucose or HbA1C. Of the other predictors considered for fasting glucose, a greater reduction in fasting glucose was seen in older veterans (p = 0.05). Medical comorbidity (measured by CCI) was the only significant predictor of HbA1C, where a higher number of diagnosed medical conditions was associated with an increase in HbA1C over time (p = 0.001).

Notably, large standard deviations were noted for reductions in both systolic (-10.41 to -4.47 at T1) and diastolic BP (-9.94 to -3.67 at T1), indicating a heterogeneity of treatment effects (HTE) within the cohort. To examine potential explanatory variables for this HTE (Table 3), we examined changes in systolic and diastolic BP outcomes by type of treatment (CPAP vs. APAP) and by race (EA vs. AA). Systolic and diastolic BP improved in veterans with either CPAP or APAP. African Ameri-
comparatively lower adherence to pharmacologic treatment, we
assessed for each time interval (SmartCard reports extracted in
OSA treatment data was available, adherence was objectively
missing data for adherence to OSA treatment
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symptoms at T1. In the subset of the cohort where adherence to
OSA treatment data was available, adherence was objectively
assessed for each time interval (SmartCard reports extracted in
average daily hours of use). The adherence was stable over time
(T1; mean ± SD = 4.90 ± 1.59, T2; mean ± SD = 4.44 ± 1.57,
(Figures 2A-C).

Table 2—Changes in outcomes with OSA treatment at Time 1 and Time 2

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Difference T1-T0, Mean (CI)</th>
<th>p-value*</th>
<th>Difference T2-T0, Mean (CI)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP</td>
<td>-7.44 (-10.41, -4.47)</td>
<td>&lt; 0.0001</td>
<td>-6.81 (-9.94, -3.67)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>-3.14 (-4.99, -1.29)</td>
<td>0.0009</td>
<td>-3.69 (-5.53, -1.85)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>10.08 (-12.33, 32.49)</td>
<td>0.38</td>
<td>2.54 (-18.83, 23.92)</td>
<td>0.81</td>
</tr>
<tr>
<td>HbA1c</td>
<td>0.10 (-0.47, 0.68)</td>
<td>0.71</td>
<td>-0.08 (-0.67, 0.83)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Difference T1, change in outcome from T0 to T1; Difference T2, change in outcome from T0 to T2; T0, 3 months preceding OSA treatment; T1, 3-6 months after OSA treatment; T2, 9-12 months after OSA treatment; Mean (CI), mean (confidence interval); BP, blood pressure; HbA1c, glycosylated hemoglobin.

*Adjusted p-value for covariates.

Table 3—Changes in blood pressure with type of treatment and by race

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Type of Treatment</th>
<th>Race</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CPAP Mean (SE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>-7.14 (1.85)</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>-2.45 (1.04)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>APAP Mean (SE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>-8.21 (2.38)</td>
<td>0.0006</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>-5.26 (1.77)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EA Mean (SE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>-5.23 (1.80)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>-1.47 (0.92)</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AA Mean (SE)</td>
<td></td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>-11.43 (2.23)</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>-6.35 (1.36)</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Change in outcome presented is from T0 to T1; T0, 3 months preceding OSA treatment; T1, 3-6 months after OSA treatment; Mean (SE), mean (standard error); CPAP, laboratory titrated fixed continuous positive airway pressure treatment; APAP, auto-adjusting positive airway pressure; EA, European Americans; AA, African Americans; BP, blood pressure. *Adjusted p-value for covariates.

Adherence to OSA Treatment
As expected in a naturalistic dataset, we encountered miss-
ing data (39% at T1 and 54% at T2) with regards to OSA treat-
ment adherence. Missing data for adherence to OSA treatment
was not significantly different by age, race, OSA severity, or
symptoms at T1. In the subset of the cohort where adherence to
OSA treatment data was available, adherence was objectively
assessed for each time interval (SmartCard reports extracted in
average daily hours of use). The adherence was stable over time
(T1; mean ± SD = 4.90 ± 1.59, T2; mean ± SD = 4.44 ± 1.57,
(p = 0.15). Adherence to OSA treatment did not correlate with
adherence to pharmacologic treatment (MPR for hypertension;
p = 0.77 or MPR for diabetes; p = 0.67). Examination of the ef-
fect of adherence to OSA treatment on primary outcomes at T1
with general linear regression showed results consistent with
previous reports, i.e., adherence to OSA treatment was signifi-
cantly associated with lower diastolic BP, HbA1C, and fasting
glucose (Figures 2A-C).

DISCUSSION
This is the first study to our knowledge to examine the ef-
effectiveness of treatment of OSA on routine clinical measures of
hypertension and diabetes control in a real-world setting. In
this cohort of hypertensive men on drug therapy, we found OSA
treatment was associated with improvement in diurnal office
systolic and diastolic blood pressure up to 1 year after initia-
tion of PAP treatment. The finding was not related to the type of
device (CPAP and APAP) used for treatment. Despite their
comparatively lower adherence to pharmacologic treatment, we
noted significant reductions in both systolic and diastolic BP
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noted significant reductions in both systolic and diastolic BP
among African Americans, while among the European Ameri-
cans, only systolic BP showed a statistically significant change.
We failed to discern any independent effects of OSA treatment
in veterans with type 2 diabetes on clinically utilized glucose
homeostasis markers: fasting glucose and HbA1C.

Clinical trials and meta-analyses indicate that
populations with higher levels of obesity (BMI) and severity
of OSA with preexisting systemic hypertension, and those
receiving antihypertensive pharmacologic therapy maybe more
likely to benefit from CPAP treatment. The magnitude of sys-
tolic and diastolic BP reduction noted in this study is higher than
has been previously reported with CPAP treatment. Studies
that recruited participants without hypertension may have en-
countered floor effects. Other characteristics of this naturalistic
cohort, which may explain these findings include; older men
(mean age 61-63 years), with a high prevalence of moderate-
severe OSA (60% to 80% with AHI/RDI > 15/h) and obesity,
a large proportion with resistant hypertension with use of ≥ 3 an-
tihypertensive medications; 59/209, 28% and multiple cardio-
vascular comorbidities (more than half had at least one of the
following: heart failure, atrial fibrillation, hypertensive heart
disease). These population characteristics have individually been
associated with higher therapeutic effects of CPAP on BP. Age and OSA interact as risk factors for hypertension: the im-
portance of age as an effect modifier of treatment response is
illustrated in this study; that is, older men showed greater OSA
treatment-related response in both systolic and diastolic BP. The
effect size (Cohen’s d for repeated measures) when considered
by type of treatment and race varied from small to large, indi-

indicating that type of treatment and race may also be significant determinants of HTE. For systolic BP changes the effect size were; CPAP = 0.49, APAP = 0.56, European Americans = 0.39, and African Americans = 0.80. For changes in diastolic BP observed, the effect size were; CPAP = 0.28, APAP = 0.50, European Americans = 0.27, and African Americans = 0.67.

The duration of treatment effect of OSA on BP is unknown, with most studies examining outcomes at a few weeks. We noted a sustained response of BP in this cohort to OSA treatment up to 12 months of follow-up. These results are consistent with a recent randomized trial of CPAP in a population with coexistent OSA and systemic hypertension. Barbe et al., reported significant but comparatively modest therapeutic effects of CPAP on systolic (-1.89 mm Hg) and diastolic BP (-2.19 mm Hg). Less than half of the participants in this study were on any drug treatment and all were asymptomatic, while the average number of antihypertensive medications per subject in this cohort was 2.67, and 40% reported daytime sleepiness.

Small efficacy studies indicate the cardiovascular risk reduction with use of APAP devices for treatment may not be equivalent to fixed-CPAP treatment. Moreover, due to lack of data, the use of APAP therapy in populations with comorbid cardiopulmonary illnesses is not recommended. The current cohort included subjects with comorbid conditions—known chronic obstructive pulmonary disease (45/221; 20%), congestive heart failure (20/221; 9%), and stroke (12/221; 5%)—were included, a previously understudied group. Our results indicate reduction in systemic BP with both APAP and CPAP treatments. These data provide a rationale to prospectively test the effectiveness of APAP treatment for titration and long-term therapy in a broader population, particularly as this technology advances.

A third of this cohort was African American, a population that suffers a higher burden of hypertension and in whom treatment of OSA is recommended as adjunctive therapy. We found significant effects on both systolic and diastolic BP that are clinically highly significant. Such treatment-related effects, if prospectively confirmed in a similar population, would have a considerable impact on cardiovascular disease. Our data do not support the effectiveness of OSA treatment in improving clinical glycemic control indices in type 2 diabetes. This maybe related to sample size or inability to adequately control for adherence in this cohort. Despite the demonstrated independent detrimental effect of OSA on the full spectrum of abnormal glucose homeostasis, data from a single randomized sham-CPAP controlled trial of CPAP (mean CPAP adherence 3.6 h nightly) in subjects with OSA and diabetes are negative. In contrast, studies with a less robust design in a similar population demonstrate a therapeutic effect of CPAP on HbA1C at 3-4 months post-treatment, suggesting an important modification of effects of CPAP on glucose homeostasis by level of adherence.

The impact of OSA treatment adherence on intermediate cardiovascular risk markers noted in this study is consistent with published reports. Nevertheless, sizable missing data on device treatment adherence limit conclusions in this study. Prospective examination of the effect modification of OSA treatment adherence on systemic BP and glucose metabolism by objective and unobtrusive measurement is crucial. A second limitation of this study pertains to selection bias (Figure 1), where the final cohort assessed for OSA treatment effects is about half of all eligible veterans. The veterans who did not follow-up at the study sites were not different with regard to available sociodemographic data, i.e. race, age, or marital status. However, there are other potential uncontrolled sources of bias that limit our results. In addition, the retrospective design imposed a burden of attrition of sample size due to missing data for key variables.

CONCLUSIONS

OSA treatment lowers blood pressure in a clinical population of men with hypertension. This study extends the known effi-
cacy to real-world effectiveness of OSA management on hypertension. Prospective effectiveness research examining changes in cardiovascular outcomes with treatment interventions for OSA is necessary to confirm these findings, to identify traits associated with a positive therapeutic response, and to inform clinical practice.

REFERENCES


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DISCLOSURE STATEMENT

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