pressure (SBP) of more than 160 mmHg, received either antihypertensive pharmacologic treatment or placebo to achieve a goal of 150/80 mmHg over a mean follow-up of 2.1 years. Patients in the treatment group received indapamide. Perindopril was added at follow-up if needed to reach blood pressure goals.

The difference in the primary outcome of fatal or nonfatal stroke was not significant between the treatment (51 events) and placebo groups (64 events) (HR 0.70; 95% CI, 0.49–1.01). Secondary endpoints included all-cause mortality, death from cardiovascular causes, and death from cardiac causes. Patients in the active treatment group had a lower rate of all-cause mortality per 1,000 patient-years (196 vs 235; HR 0.79; 95% CI, 0.65–0.95; NNT=44). Differences in other secondary outcomes were not significant.

A separate 2008 RCT evaluated the effect of SBP control in 4,418 hypertensive Japanese patients 65 to 85 years of age, of whom 1,869 were 75 to 85 years old. Hypertension was defined as a SBP of more than 160 mmHg. Patients were randomized to strict (≤140 mmHg) or mild (SBP 140–160 mmHg) treatment groups. Patients were treated with efonidipine; other antihypertensive medications were added as needed.

No significant differences were found between the strict and mild control groups for all-cause mortality (0.41% vs 0.36%; P=.81), cerebrovascular disease (2.35% vs 2.2%; P=1.00), cardiac and vascular disease (1.18% vs 1.27%; P=.53), and renal failure (0.36 vs 0.41%; P=.32).

A 2010 RCT of 3,260 patients aged 70 to 84 years (average, 76.1±4.1 years) with isolated systolic hypertension (>160 mmHg) were randomized to strict (SBP ≤140 mmHg) or moderate (SBP 140–165 mmHg) treatment groups. Patients were treated with valsartan as the first step. If goals were not reached, investigators increased the valsartan dose or added another agent to achieve goal a SBP at or below 160 mmHg. The primary endpoint was a composite of cardiovascular events. Analysis was by intention to treat.

No significant differences were found in cardiovascular events (2.4% vs 2.3%; HR 1.04; 95% CI, 0.56–1.93) or all-cause mortality (1.55% vs 1.96%; HR 0.78; 95% CI, 0.46–1.33).

The 2014 Eighth Joint National Committee (JNC 8) guidelines recommended a target SBP less than 150 mmHg and diastolic blood pressure less than 90 mmHg for adults 60 years of age or older. Similarly, the National Institute of Health and Care Exchange (NICE) recommend a goal of 150/90 mmHg or lower for adults 80 years of age or older.

Is paroxetine a safe and effective treatment for vasomotor symptoms?

Evidence-Based Answer

From a baseline of 6 to 12 hot flashes per day, paroxetine decreases the frequency of vasomotor symptoms by approximately 1 to 2 hot flashes per day over placebo and decreases the severity slightly. Paroxetine has a low incidence of serious adverse events (SOR: A, RCTs with homogeneous results). Paroxetine decreases nighttime awakenings attributed to vasomotor symptoms more than placebo (SOR: B, single RCT).

A 2013 RCT (n=1,184) evaluated the effect of paroxetine on hot flash frequency in otherwise healthy postmenopausal women (age range, 40–79 years; median, 54 years; 70% white, 27% black, 3% other) with an average of at least 7 to 8 moderate to severe hot flashes per day over placebo (SOR: A, RCTs with homogeneous results). Patients were excluded if they had previously used selective serotonin reuptake inhibitors or selective serotonin-norepinephrine reuptake inhibitors without benefit for vasomotor symptoms. Patients were divided into 12- or 24-week arms and further divided to receive paroxetine 7.5 mg daily or placebo. Hot flash frequency and intensity (mild, moderate, or severe) were recorded daily in a validated electronic diary. The severity score ranged from 2 (all non-mild hot flashes were moderate) to 3 (all non-mild hot flashes were severe).

Paroxetine decreased moderate to severe hot flash frequency more than placebo at weeks 4 and 12 (see TABLE 1). Paroxetine increased “persistence of treatment benefit,” defined as a 50% or greater reduction in hot flash frequency.
in hot flash frequency at 24 weeks, versus placebo (48% vs 36%; \( P = .0066 \)). Paroxetine also decreased hot flash severity at 4 weeks, but inconsistently at 12 weeks (see TABLE 2).

A separate report of the same study showed paroxetine decreased nighttime awakenings attributed to vasomotor symptoms more than placebo (baseline: 3.6 awakenings/night) at 4, 12, and 24 weeks (see TABLE 2).\(^4\) Mild to moderate adverse events occurred frequently in both groups (50% with paroxetine vs 47% with placebo).

A 2005 RCT (N=151) evaluated the effect of paroxetine on hot flash frequency in women who had at least 14 hot flashes per week (mean daily baseline 7–8) for a minimum of 30 days (>12 months in 65%).\(^2\) Median age was early 50s (range 27–76 years), 98% were peri- or postmenopausal, more than 80% had a history of breast cancer, and 60% were taking an anti-estrogen agent. Patients with serum creatinine or bilirubin concentrations of more than twice normal were excluded. Patients were randomized to receive paroxetine (10 or 20 mg daily) or placebo for 4 weeks followed by crossover to the opposite arm for another 4 weeks with no washout. Hot flash frequency and intensity were recorded daily in a validated diary (29% were excluded from the analysis due to incomplete or missing diaries). A composite score was calculated by adding the number of hot flashes after multiplying by 1, 2, 3, or 4 for each mild, moderate, severe, or very severe hot flash, respectively.

Both doses of paroxetine decreased hot flash frequency more than placebo (see TABLE 1). Paroxetine increased the percent reduction in composite score from baseline to end of treatment versus placebo (46% vs 14%, \( P < .001 \) for 10 mg; 56% vs 29%, \( P < .001 \) for 20 mg). Paroxetine 20 mg increased nausea compared with placebo (41% vs 10%; \( P < .001 \)), which was the only statistically significant difference in adverse events.

A 2003 RCT (N=165) measured reduction in hot flash composite score (primary outcome) and frequency (secondary outcome) in postmenopausal women (age range, 36–76 years; mean, 54 years; 87% white, 12% black, 1% other).\(^3\) Patients had to have at least 2 to 3 hot flashes daily (14 per week). Approximately 7% of patients had a history of breast cancer. Patients were randomized to receive paroxetine controlled release (CR) 12.5 mg, paroxetine CR 25 mg, or placebo for 6 weeks. Hot flash frequency and intensity were recorded daily in a validated diary. The composite score was calculated as in the trial above with a baseline of 14 to 17 in the 3 arms.

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**TABLE 1**

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose (mg)</th>
<th>Duration (weeks)</th>
<th>Patients, N</th>
<th>Baseline no. of daily hot flashes</th>
<th>Change in no. of daily hot flashes</th>
<th>Mean difference (( P ) value or 95% CI)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intervention</td>
<td>Control</td>
<td>Intervention</td>
</tr>
<tr>
<td>1</td>
<td>7.5</td>
<td>4</td>
<td>606</td>
<td>12</td>
<td>12</td>
<td>-4.7</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>4</td>
<td>76</td>
<td>12</td>
<td>12</td>
<td>-6.2</td>
</tr>
<tr>
<td>2</td>
<td>12.5 CR</td>
<td>6</td>
<td>107</td>
<td>7.1</td>
<td>6.6</td>
<td>-3.3</td>
</tr>
<tr>
<td>2</td>
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<td>6</td>
<td>114</td>
<td>6.4</td>
<td>6.6</td>
<td>-3.2</td>
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</tbody>
</table>

**TABLE 2**

<table>
<thead>
<tr>
<th>Outcome:</th>
<th>Change in severity (baseline 2.5 on a scale of 2–3)</th>
<th>Decrease in nighttime awakenings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration:</td>
<td>12-week arm</td>
<td>24-week arm</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Paroxetine</td>
<td>Placebo</td>
</tr>
<tr>
<td>4 weeks</td>
<td>-0.09</td>
<td>-0.05</td>
</tr>
<tr>
<td>12 weeks</td>
<td>-0.10</td>
<td>-0.09</td>
</tr>
<tr>
<td>24 weeks</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

\(^a\)Not statistically significant. NR=not reported.
Both doses of paroxetine decreased hot flash frequency (see TABLE 1) and composite score (MD –4.7; 95% CI –8.1 to –1.3 for 12.5 mg CR; and MD –3.6; 95% CI –6.8 to –0.4 for 25 mg CR) more than placebo. Adverse events occurred frequently in both groups (58% with paroxetine vs 54% with placebo), but no statistically significant differences were noted in the 8 most common adverse events.

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### Is there an association between prenatal acetaminophen use and development of asthma?

**Evidence-Based Answer**  
There does appear to be an association between maternal prenatal acetaminophen use and the risk of developing childhood wheezing and asthma (SOR: B, systematic review of cohort studies and individual cohort studies).

A 2014 systematic review of observational cohort studies of acetaminophen use during pregnancy and early childhood identified 5 studies that focused on acetaminophen use during pregnancy (N=220,825).1 Two of these studies obtained exposure data prospectively during pregnancy.

An association was found between exposure to acetaminophen during the first trimester and development of childhood asthma (pooled OR 1.4; 95% CI 1.0–1.9). Conflicting results were seen in 2 studies of exposure during the second trimester (1 retrospective, n=12,733; OR 1.1; 95% CI, 0.9–1.2; and 1 prospective, n=8,511; OR 2.2; 95% CI, 1.2–3.9). A total of 14,238 patients in 2 studies, 1 prospective, of exposure during the third trimester suggested a weak association between acetaminophen exposure and development of asthma (pooled OR 1.2; 95% CI, 1.0–1.3), while 3 retrospective studies combining exposure during the second and third trimester supported a stronger association (n=883,091; pooled OR 1.5; 95% CI, 1.4–1.6).1

Pooled analysis was not completed for 3 studies that included data for exposure during the entire pregnancy because of significant heterogeneity. Application of these results is limited due to the small number of studies, high between-study heterogeneity, and various potential confounders, including effects of adjustment for respiratory infections during pregnancy.1

A cohort study in western Sweden included 4,496 respondents to questionnaires about maternal prenatal acetaminophen intake obtained retrospectively when the child was 6 months old, incidence of recurrent wheeze in children after birth, and treatment with inhaled corticosteroids (ICS).2 In a multivariate analysis, the risk of ICS-treated wheeze at 4.5 years of age was significantly increased by prenatal exposure to acetaminophen (OR 1.6; 95% CI, 1.0–2.6). However, the survey response rate was low, at 55%.

Lastly, a prospective birth cohort study in New York of 301 children of Dominican Republic and African American ethnicity evaluated risk of wheezing related to prenatal acetaminophen use.3 Prenatal use of acetaminophen by mothers, obtained by questionnaire during the third trimester, predicted an increase in current wheeze at 5 years of life when adjusted for sex, ethnicity, birth order, maternal asthma, maternal hardship, environmental tobacco smoke exposure, and postnatal acetaminophen use (RR 1.7; 95% CI, 1.2–2.4). Polymorphism with a minor allele for glutathione S-transferase Pi modified this risk consistent with a possible mechanism involving the glutathione pathway.

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