Antidepressant Use During Pregnancy & Lactation

**Author:** Beth Arnold, PharmD, Reviewed by: Greg Simon, MD, MPH; Annelise Gaaserud, MD, MPH

**Key Points:**
- Selective Serotonin Reuptake Inhibitors (SSRIs) have the most data for use during pregnancy and lactation.
- Antidepressant exposure during pregnancy has been associated with:
  - No confirmed risk of birth defects, except cardiac defects with paroxetine in the 1st trimester (2/1000 births)
  - Modest increased risk of spontaneous abortion, preterm birth and low birth weight
  - Small increased risk of persistent pulmonary hypertension with 3rd trimester exposure (6-12/1000)
  - Neonatal adaptation syndrome in up to 30% of babies with 3rd trimester exposure
  - No long-term developmental effects (based on limited data)
  - The benefits of breast feeding generally seem to outweigh the risks.
- The potential risks of medication exposure must be balanced with potential harms of untreated maternal depression.
- For more information, visit the [KPWA Depression Guideline](https://www.kpw.org/).
Assessing the benefits and risks of taking an antidepressant during pregnancy and lactation is challenging because the evidence is limited to observational studies that are subject to confounding and bias. Many of the adverse effects associated with medication use have also been observed in higher rates in mothers with untreated depression likely related to underlying risk factors associated with the disease itself, related comorbidities and/or lifestyle factors. The current evidence cannot separate these risks from the effect of the medication exposure. In addition, information about the daily dosage, duration of exposure and concomitant use of other medications is often incomplete.

During pregnancy, women with depression have a high risk of relapse whether they are on or off medications; approximately 68% relapse off medication compared with 26% who continue antidepressants. Untreated maternal depression has been associated with miscarriage, increased preterm birth, low birth weight, increased rates of cigarette, alcohol and other substance misuse, and poor prenatal care. In the postpartum period, there is a greater risk of disturbance in the development of the maternal-infant bond in severely depressed mothers; in addition, postpartum depression has been associated with lower IQ, slower language development, increased risk of ADHD and an increased risk of psychiatric illness in the child. Decisions about the use of antidepressant therapy during pregnancy and lactation must be individualized to the patient.

**Antidepressant use during pregnancy**

**Major congenital malformations**

Consistent evidence indicates that the SSRIs are associated with an overall risk of major congenital malformations comparable to the risk reported in the general population (1-3%). Controversy remains about the risk of cardiovascular malformations with paroxetine in first trimester exposure; however, if true, the absolute risk is small (2/1000 births). Likewise, two studies have reported an increased risk of heart defects with bupropion, but this has not been confirmed in other studies. The risk profile of venlafaxine appears similar to the SSRIs.

**Spontaneous abortion**

Spontaneous abortion is common in the general population, occurring in 8-20 per 100 clinically detected pregnancies during the first 20 weeks. Studies suggest that the use of antidepressants during the first trimester is associated with a modestly raised risk of spontaneous abortion with odds ratios in the range of 1.4-1.6.
**Preterm birth and low birth weight**

In 2016 in Washington state, the rate of preterm birth (<37 weeks gestation) was 8 per 100. Evidence suggests that about 9% of babies born to mothers who take SSRIs during pregnancy will be born early (before 36 weeks). In the United States in 2014, the rate of low birthweight (<2,500 grams) was also 8 per 100. The studies evaluating the association between antidepressant exposure and low birth weight have been inconsistent.

**Persistent pulmonary hypertension (PPHN)**

PPHN occurs in 1-2 per 1000 births in the general population. An early study suggested a six-fold increased risk with SSRIs; however, subsequent studies have not confirmed this finding. In 2011, the FDA changed the warning indicating that it is unclear whether the use of SSRIs during pregnancy can cause PPHN. If SSRI use does increase the odds of PPHN by 6, the absolute risk is small (6-12 per 1000 births). The potential risk of PPHN with venlafaxine and bupropion exposure requires further confirmation.

**Neonatal adaptation syndrome (NAS)**

NAS is characterized by irritability, jitteriness, respiratory distress, seizures, and/or low blood sugar. It has been observed in up to 30% of babies exposed to SSRIs and SNRIs and appears to be more common in babies exposed to paroxetine, venlafaxine and multiple medications (e.g., antidepressant + benzodiazepine). In most babies, the symptoms are mild and treated conservatively with monitoring of the baby, symptomatic support, increased skin-to-skin contact, and swaddling. The etiology of NAS is unclear and may represent either neonatal toxicity or a withdrawal syndrome. It is unclear whether tapering the antidepressant prior to delivery decreases the risk of NAS.

**Long-term developmental effects**

There are no good studies about the long-term effects of SSRI exposure in pregnancy. Only small, less rigorous studies are available and seem to indicate no effects on the child’s behavioral, language, or IQ development.

**Antidepressant use during lactation**

The benefits of breastfeeding for the baby are well documented and probably outweigh any risks of SSRIs. Accumulated data indicate that the risk of adverse events in the nursing full-term infant is low, and the benefits of breastfeeding seem to generally outweigh potential risks. The risk of drug accumulation and associated toxicity may be higher in premature infants or in infants with signs of compromised hepatic metabolism. Available data suggest that all antidepressants are excreted into breast milk and the drug
concentration in breast milk is largely determined by the maternal serum drug concentration. To minimize the risk to the baby, use the minimum medication dose that provides adequate control of the mother’s symptoms. There does not appear to be any benefit to altering the timing of nursing, or selectively discarding portions of the breast milk, to minimize the drug exposure to the baby.

Infant drug exposure is generally higher through placental passage than through breast milk. Thus, if a woman has taken an antidepressant during pregnancy, it generally makes sense to continue with that antidepressant during breastfeeding to minimize the number of medications the infant is exposed to. There is some literature that suggests the exposure to low antidepressant levels in breast milk could help prevent neonatal adaptation syndrome in the baby shortly after birth.

Most experts recommend sertraline during the third trimester and during breastfeeding because of its short half-life and the relatively low drug levels found in cord blood and breast milk.

Paroxetine has low drug levels in breast milk, and is a reasonable option if the drug is started after the 2nd trimester or in the postpartum period.

Fluoxetine, citalopram, and escitalopram (which have higher breast milk and plasma concentrations) are usually okay during breastfeeding for patients who had good results with these medications during pregnancy. Due to a higher relative proportion in breast milk and long half-life, babies that are exposed to fluoxetine may be at risk for developing feeding problems and colicky behavior. Data for escitalopram is limited.

Based on limited data, venlafaxine has not been associated with adverse events in the infant; however, because relatively high infant doses were observed in one study, close observation of adverse events in the infant is recommended.

Based on limited data, maternal doses of bupropion up to 300 mg daily produce low levels in breastmilk and are not expected to cause adverse events; however, there are case reports of possible seizure in partially breastfed 6-month olds & close monitoring is recommended.

**Recommendations for choice of drug therapy in pregnancy or breastfeeding mother**

In a patient who is not currently receiving drug therapy, sertraline is the drug of first choice because literature supports use during pre-conception, the 1st trimester, and during pregnancy and lactation. However, if sertraline is not an option (e.g., patient previously failed an adequate dose and duration or experienced intolerable side effects), any of the medications where literature
supports use (green) are reasonable alternatives (Table 1).

In a patient who is on well established, effective therapy, it is reasonable to continue any of the medications where literature supports use (green) or where absolute risks are likely small (yellow) as the benefit of continuing therapy likely outweighs the risk of switching. However, consideration should be given to switching therapy if the patient is taking a medication where there is possible evidence of harm (red). In a patient who is not responding to current therapy, sertraline is again the drug of first choice, unless the patient had a previous trial.

For more information, see the **KPWA Depression Guideline**. For patient specific consultations, refer to your local behavioral health or obstetrics service or call the Mind Phone (1-888-844-4662).

**Table 1.** Summary of Literature Supporting Use of Antidepressants in the Various Stages of Pregnancy

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Pre-conception</th>
<th>1st Trimester</th>
<th>3rd Trimester</th>
<th>Post-partum &amp; Lactation</th>
<th>Estimated % of Maternal Dose to Baby via Breast Milk**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sertraline</td>
<td>😊</td>
<td>😊</td>
<td>😊</td>
<td>😊</td>
<td>0.4% - 2.3%</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>😊</td>
<td>😊</td>
<td>😊</td>
<td>😊</td>
<td>1.2% - 12.0%</td>
</tr>
<tr>
<td>Citalopram</td>
<td>😊</td>
<td>😊</td>
<td>😊</td>
<td>😊</td>
<td>0.7% - 9.0%</td>
</tr>
<tr>
<td>Escitalopram†</td>
<td>😊</td>
<td>😊</td>
<td>😊</td>
<td>😊</td>
<td>3.9% - 7.9%</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>😒</td>
<td>😒</td>
<td>😊</td>
<td>😊</td>
<td>0.1% - 4.3%</td>
</tr>
<tr>
<td>Venlafaxine†</td>
<td>😊</td>
<td>😊</td>
<td>😒</td>
<td>😒</td>
<td>3.5% - 8.1%</td>
</tr>
<tr>
<td>Bupropion†</td>
<td>😒</td>
<td>😒</td>
<td>😒</td>
<td>😒</td>
<td>0.2% - 2%</td>
</tr>
</tbody>
</table>

😊 = Current literature supports use; 😊 = Caution but absolute risks likely small; 😒 = Possible evidence of harm
†Limited data **Weight-adjusted estimates that include the agent and its active metabolites.
The Impact of Drug Coupons & Copay Cards

By Emily Peltier, Pharmacist Intern; Reviewed by Sara Forrester, PharmD, MS, Bryan Davis, PharmD

Key Points:

- Drug coupon and copay card use is becoming more common. Between 2007 and 2010, the purchase of drugs with coupons doubled, from 26% to 54%, and continues to rise.
- Coupons reduce patient cost sharing but have negative downstream effects, including increased drug price, reduced generic uptake, and increased brand name drug sales leading to an increased overall drug spend.
- States have proposed legislation to ban prescription coupon use to eliminate the negative effects on drug cost. KPWA has taken a similar stand and does not generally accept coupons for branded products.
- KPWA has the Medical Financial Assistance (MFA) program in place to help members and non-members in need with medication costs.

Background

- Between 2009 and 2014, high-deductible health plan enrollment has tripled.
- Health plan benefit design utilizes several strategies to reduce costs, including tiered formularies and cost sharing.
- Many pharmaceutical companies distribute copay cards and coupons for brand name medications, targeting patients with high-deductible plans.
- Coupon cards are positive for patients in the short-term as they remove most, if not all, of the patient’s cost-share, but have negative consequences in the long-term, such as increased premiums.
- By removing cost shares, patients are no longer impacted by medication tiering or other benefit design strategies. Drug coupons effectively remove financial incentives for the patient to use the most cost-effective drug.
- Since coupons are only for branded medications, patients are incentivized to use a more costly, non-preferred medication, often when there is a generic available. This is because coupons may remove the cost share completely whereas the generic medication is subject to a generic cost share.
- Legislation has been proposed in several states to control coupon use with the intent of reducing drug spend and eliminating other negative effects of coupons, such as increasing drug prices.
Coupon Impact Study

- A 2016 study recently studied the impact of drug coupons on the utilization of generic drugs.
- An internet coupon database was matched to prescription count data and pharmacy claims data to identify 29 drugs with a coupon and a bioequivalent generic from June 2007 to December 2010.
- Difference-in-difference and triple difference models were used with additional statistical modeling techniques to analyze the 29 drugs with a coupon compared to a group of 56 drugs with no coupon.
- The primary outcome was “generic efficiency”, or generic dispensing rate (the percent of prescriptions dispensed with a generic product out of all prescriptions with a generic equivalent available).

Results

- The prevalence of copay coupons doubled over the study period (Figure 1).
- The price of drugs with coupons grew an average of 12-13% per year compared to the group without coupons at 7-8% per year.
- Generic efficiency was significantly reduced by drug coupons (Table 2).
- Coupons increased the sale of brand name products by 60% by reducing sales of their generic counterparts.
- Average drug spend increased by 1.2-4.6% following the utilization of coupons. For an average drug, this increase would be between $6 million and $24 million per year.

![Figure 1. Share of Brand Spending with a Coupon Available, 6/2007—12/2010](image-url)
Table 2. Intensity of Coupon and Generic Efficiency

<table>
<thead>
<tr>
<th></th>
<th>Generic Efficiency</th>
<th>Percentage</th>
<th>Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No coupon</td>
<td></td>
<td>92.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-intensity coupon*</td>
<td></td>
<td>84.5%</td>
<td>↓ 7.5%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>High-intensity coupon*</td>
<td></td>
<td>80.6%</td>
<td>↓ 11.4%</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

*Intensity determined by dividing the value of each coupon by average consumer copay. The median intensity value for the sample was 0.91. Low-intensity < 0.91; High-intensity ≥ 0.91

Legislation

- Government plans, Medicare, and Medicaid, do not allow the use of coupons because they are considered illegal kickbacks.
- Massachusetts was the only state to pass a law that banned certain copay coupons, but the ban was eliminated in 2012.
- California and New Jersey are proposing laws to ban the use of drug coupons and copay cards to allow the cost-savings initiatives of health plan benefit design to continue to reduce drug costs and encourage use of bioequivalent generics.

KP Medical Financial Assistance (MFA) Program

- The Medical Financial Assistance (MFA) is designed to help underprivileged patients pay for their medical expenses and medications for families with income at or below 300% of the Federal Poverty Guidelines (FPG).
- This is for use with formulary agents only.
- Additional resources can be found on the MFA homepage including policies and applications.

Conclusion

- Coupons may benefit the patient in the short-term by covering their cost shares, but ultimately leads to increased drug spend and higher premiums.
- KPWA takes a general stance of not accepting coupons to help control costs and provide the lowest premiums to the member.
- KPWA’s MFA program exists to help cover the medical expenses and medications for the populations with the greatest need.
- Please refer your patients in need of financial assistance to the MFA application.
Osteoporosis and Fracture Management

By Mackhai Nguyen, Pharmacy Intern; Edited by Tiffany Nguyen, PharmD

Key Points:
• A review of medications should be conducted for patients with osteoporosis to reduce exposure to fracture-promoting drugs and to ensure that patients are appropriately treated.
• Emphasize the importance of adherence to osteoporosis medications. Patients who are highly adherent to their medications have shown over a 15% reduction in fracture rates compared to those with low adherence.

Background
• Kaiser Permanente of Washington underperforms on the HEDIS measure for osteoporosis management.
  ⇒ The measure assesses the proportion of women aged 65-85 years who suffered a fracture and within 6 months of the fracture, underwent a DEXA scan, or filled a prescription for a bone-density increasing drug such as a bisphosphonate.
  ⇒ As of September 2016, KPWA’s performance on this measure was 42.9%, which is below our target of 67.5% to be within the 90% percentile among health plans.
  ⇒ KPWA’s osteoporosis guideline and Clinical Pearls are available on our website as a resource.

Medication Use Post-Fracture
• Prescription drugs are a potentially modifiable risk factor for fractures. Many commonly prescribed drugs have been found to increase fracture risk, either by increasing risk of falls or by lowering bone density (Table 1).
• Using pharmacy claims data, a retrospective cohort study of Medicare members (N=168,133) assessed the use of prescription drugs in the 120 days before and after a fragility fracture.
  ⇒ Only 20% of patients filled a prescription for a bone-density increasing drug (e.g., bisphosphonates) in the 120 days prior to the fracture event. Post-fracture, the use of these medications increased slightly by 2% (P<0.001).
  ⇒ 76% of patients were exposed to a non-opiate drug that increases risk of fracture the 120 days prior to the fracture. Within 120 days after the fracture, the proportion of patients on these fracture-promoting drugs increased slightly to 78%. Post-fracture use of opiates increased across all fracture locations (hip, wrist, and shoulder), possibly due to pain associated with the event.
Table 1. Drugs Associated with Increased Risk of Fracture by Mechanism

<table>
<thead>
<tr>
<th>Increased Risk of Falls</th>
<th>Decreased Bone Density</th>
<th>Unclear Primary Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>Inhaled glucocorticoids</td>
<td>Atypical antipsychotics</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Oral glucocorticoids</td>
<td>Typical antipsychotics</td>
</tr>
<tr>
<td>Sedative-hypnotics (non-benzo)*</td>
<td>PPIs*</td>
<td>Loop diuretics</td>
</tr>
<tr>
<td>SSRIs*</td>
<td>H2RAs</td>
<td></td>
</tr>
<tr>
<td>TCAs</td>
<td>Thiazolidinediones</td>
<td></td>
</tr>
<tr>
<td>Anti-Parkinson disease drugs</td>
<td>Anticonvulsants</td>
<td></td>
</tr>
<tr>
<td>Centrally acting antihypertensives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonnitrate anti-anginal agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioids</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Subset of drugs with a risk of fracture most strongly supported by existing literature. SSRI = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants; PPIs = proton-pump inhibitors; H2RAs = histamine receptor antagonists

Challenges to Medication Adherence

- Patients who are highly adherent (defined as drug available on hand ≥80% of time) to osteoporosis treatments showed a 16% reduction in fracture rate (average 2 year follow-up) compared to patients with low adherence (p<0.005).
- However, many patients stop taking their medications over time, with a large number stopping within the first year.
- According to a retrospective cohort study of commercially insured patients (N=88,571 females and N=41,984 males), the average 12-month adherence to osteoporosis treatments post-fracture was 56% in females and 61% in males. The most common therapy was oral bisphosphonates (75.8%).
- In another survey of 1,407 postmenopausal women in the U.S. with self-reported osteoporosis, 503 (36%) were never treated. Most common reasons reported for not choosing to receive treatment were fear of side effects from prescription products and using an over-the-counter vitamins/supplements instead (Table 2).
• Thus, providers should encourage patients to initiate and adhere to osteoporosis medications (Table 3).
  ⇒ Discuss the benefits and risks of treatment options, and address patient concerns.
  ⇒ Table 4 provides counseling points for adverse events associated with bisphosphonates.

Table 2. Reasons for Non-Treatment and Reasons for Discontinuation

<table>
<thead>
<tr>
<th>Reason for Non-Treatment</th>
<th>Response N = 503</th>
<th>Reason for Discontinuation</th>
<th>Response N = 323</th>
</tr>
</thead>
<tbody>
<tr>
<td>Took over-the-counter vitamins and supplements instead</td>
<td>57.5%</td>
<td>Provider told me to stop</td>
<td>41.2%</td>
</tr>
<tr>
<td>Fear of side effects</td>
<td>43.9%</td>
<td>Concerned about long-term safety</td>
<td>30.3%</td>
</tr>
<tr>
<td>Tried lifestyle changes instead</td>
<td>37.8%</td>
<td>Experienced side effects</td>
<td>29.7%</td>
</tr>
<tr>
<td>Osteoporosis not serious enough to require prescription medication</td>
<td>24.3%</td>
<td>Heard negative news reports</td>
<td>24.5%</td>
</tr>
</tbody>
</table>

Table 3. Osteoporosis Treatment Options

<table>
<thead>
<tr>
<th>Line of Therapy</th>
<th>Medication</th>
<th>Formulary Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>Alendronate</td>
<td>Formulary</td>
</tr>
<tr>
<td></td>
<td>Risedronate</td>
<td>Formulary [ST]</td>
</tr>
<tr>
<td>2nd</td>
<td>Zoledronic acid</td>
<td>Medical benefit</td>
</tr>
<tr>
<td>3rd</td>
<td>Denosumab</td>
<td>Medical benefit [PA]</td>
</tr>
<tr>
<td></td>
<td>Raloxifene</td>
<td>Formulary [PA]</td>
</tr>
<tr>
<td></td>
<td>Calcitonin</td>
<td>Non-formulary</td>
</tr>
<tr>
<td></td>
<td>Teriparatide</td>
<td>Non-formulary [PA]</td>
</tr>
</tbody>
</table>

PA = prior authorization; ST = step therapy
Table 4. Adverse Events (AE) Associated with Bisphosphonates

<table>
<thead>
<tr>
<th>AE</th>
<th>Symptoms</th>
<th>Risk</th>
<th>Counseling Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Abdominal pain; dyspepsia; nausea; flatulence; gastritis</td>
<td>12.6%*</td>
<td>• Take the medication in the morning &gt;30 minutes before food with a full glass (8 oz.) of plain water. \n• Do not lie down &gt;30 minutes after taking the medication. \n• Zoledronic acid (IV bisphosphonate) is an alternative option for those who have difficulty tolerating the oral formulation.</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>Bone, joint, and/or muscle pain</td>
<td>3.1%*</td>
<td>• In those who develop severe pain, bisphosphonates should be discontinued.10</td>
</tr>
<tr>
<td>Osteonecrosis of the jaw</td>
<td>Pain, swelling, or redness of gums; loose teeth; numbness in the jaw; visible bone in the mouth</td>
<td>0.0001%**</td>
<td>• Very rare and if seen, typically in patients with cancer or compromised immune system who are treated with high doses of IV bisphosphonates.</td>
</tr>
</tbody>
</table>

*Rates from a 1-year, double-blind, multicenter study assessing dose of alendronate 70 mg weekly in postmenopausal women; **Risk for oral bisphosphonates.

Asthma Misdiagnoses and Remissions: Reassessing Asthma Diagnoses

By Bryan Davis, PharmD; Reviewed by Mark La Shell, MD and Lisa Nguyen, PharmD, BCPS

Key Points:
• A cohort study of adult patients who were previously diagnosed with asthma within the last five years found that a third had a misdiagnosis of asthma, and a small minority went into spontaneous asthma remission.
Approximately 25% of patients using asthma controller medications had asthma ruled out, were tapered off all or some asthma medications, and remained free of asthma symptoms 12 months after.

Due to the complexity of the disease and the potential for alternative explanations for symptoms other than asthma, asthma diagnosis should be reassessed regularly.

Ruling out asthma can reduce unnecessary exposure to side effects of medications, reduce the cost burden to the patient, and possibly discover a serious misdiagnosis.

Background

Asthma is a disease characterized by episodic airflow obstruction or limitation which is at least partially reversible, inflammation in the lung airways, and bronchial hyperresponsiveness.

Asthma is generally considered a chronic disease that has different clinical presentations and variable ages of onset. Occurrences of remission have been observed, with higher rates of remission after childhood onset.

Many studies have investigated the factors involved in asthma remission, particularly from childhood onset, but there is less evidence regarding remissions in adult-onset asthma.

Study Population and Interventions

A recent Canadian study (n=701) evaluated remission rates and misdiagnosis rates in patients aged 18 years and older with adult-onset asthma diagnosis.

Details of inclusion and exclusion criteria are in Table 4.

Mean age of study participants was 50 years (SD of 16 years), and approximately two-thirds were female.

Participants were studied over 12 weeks using an objective, diagnostic algorithm over 4 visits.

Participants with a negative bronchial challenge test result at visit 2 who were using daily asthma-controlling medications had their controller medications decreased. If bronchial test was still negative at visit 3, participants were tapered off some or all asthma medications.

Pulmonologist assessments were conducted to confirm or rule out current asthma. Patients with no evidence of current asthma underwent workup to determine alternative diagnoses and were reassessed after 1 year.
Table 4. Study Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥18 years old, diagnosed with asthma within 5 years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-term oral steroids use</td>
</tr>
<tr>
<td>Pregnant or breastfeeding</td>
</tr>
<tr>
<td>Unable to perform spirometry or contraindication to a bronchial challenge test*</td>
</tr>
<tr>
<td>A smoking history greater than 10 pack-years</td>
</tr>
</tbody>
</table>

*Contraindications included known aortic or cerebral aneurysms, or history of myocardial infarction or stroke within 3 previous months

Characteristics of Patients with Ruled-out Asthma

- 382 (62.3%) out of 613 participants who completed the study were confirmed to have current asthma during the 4-visit diagnostic assessment period, and current asthma was ruled out in 203 (33.1%) participants.
- 185 (91%) out of 203 participants with ruled-out asthma were found to have alternative diagnoses (e.g., asymptomatic asthma, rhinitis, anxiety, obesity). Approximately 13% were reconfirmed to have asthma, and 6% (2% of entire cohort) were found to have a serious cardiorespiratory condition that was missed (Table 5).
- Compared to those with confirmed asthma, patients with ruled-out asthma were significantly more likely to have the following characteristics (Table 6):
  - No improvement in post-bronchodilator lung function, defined as an increase of ≥12% FEV<sub>1</sub> (forced expiratory volume in the first second of expiration) and ≥200 mL (21%)
  - No spirometry performed at the time of asthma diagnosis (14.1%)
  - No use of controller asthma medications (14.3%)
  - No history of wheezing within the last 12 months (14.7%)
Table 5. Alternative Diagnoses in Patients with No Airflow Obstruction after Medication Taper

<table>
<thead>
<tr>
<th>Top Diagnoses (N=203)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>61 (28.6)</td>
</tr>
<tr>
<td>Allergic or non-allergic rhinitis</td>
<td>54 (25.3)</td>
</tr>
<tr>
<td>GERD</td>
<td>18 (8.5)</td>
</tr>
<tr>
<td>Anxiety or hyperventilation</td>
<td>8 (3.8)</td>
</tr>
<tr>
<td>Deconditioning</td>
<td>7 (3.3)</td>
</tr>
<tr>
<td>Obesity or Eosinophilic bronchitis</td>
<td>6 (2.8)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>4 (1.9)</td>
</tr>
<tr>
<td>COPD</td>
<td>4 (1.9)</td>
</tr>
<tr>
<td>Chronic cough due to ACE inhibitors</td>
<td>4 (1.9)</td>
</tr>
<tr>
<td>Post-viral cough</td>
<td>4 (1.9)</td>
</tr>
<tr>
<td>Serious Cardiorespiratory Conditions (4 ischemic heart disease, 2 subglottic stenosis, 2 bronchiectasis, 1 interstitial lung disease, 1 pulmonary hypertension, 1 sarcoidosis, 1 tracheobronchomalacia)</td>
<td>12 (5.9)</td>
</tr>
</tbody>
</table>

ACE= angiotensin-converting enzyme; COPD=chronic obstructive pulmonary disease; GERD=gastroesophageal reflux disease

Table 6. Characteristics of Patients with Confirmed Asthma versus Ruled-Out Asthma

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Confirmed Asthma N (%)</th>
<th>Ruled-Out Asthma N (%)</th>
<th>Absolute Difference (95% CI), p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-bronchodilator improvement in FEV₁,*</td>
<td>86 (21.0)</td>
<td>0</td>
<td>21.0 (17.1 to 25.0), &lt;0.001</td>
</tr>
<tr>
<td>Patient had spirometry at time of diagnosis</td>
<td>298 (72.7)</td>
<td>119 (58.6)</td>
<td>14.1 (6.0 to 22.1), &lt;0.001</td>
</tr>
<tr>
<td>Currently using asthma medications</td>
<td>370 (90.2)</td>
<td>161 (79.3)</td>
<td>10.9 (4.7 to 17.2), &lt;0.001</td>
</tr>
<tr>
<td>Using asthma-controlling medications daily</td>
<td>202 (49.3)</td>
<td>71 (35.0)</td>
<td>14.3 (6.1 to 22.4), &lt;0.001</td>
</tr>
<tr>
<td>Wheezing during past 12 months</td>
<td>337 (82.2)</td>
<td>137 (67.5)</td>
<td>14.7 (7.3 to 22.1), &lt;0.001</td>
</tr>
</tbody>
</table>

*FEV₁=forced expiratory volume in the first second of expiration, with improvement by ≥12% and ≥200 mL
One Year Follow-Up after Ruling-Out Asthma

- 22 (10.8%) of 203 participants in whom current asthma had been ruled out had a positive bronchial challenge test result at either 6 or 12 months. Of the 22 participants,
  - 16 were asymptomatic and did not resume use of their asthma medications
  - 6 participants resumed treatment with asthma medications
  - 1 participant was treated with a course of oral corticosteroids
- The remaining 181 participants (29.5% of the cohort) exhibited no clinical or laboratory evidence of asthma during the 12 months of follow-up.
- Since patients were only followed for up to 15 months, it is possible they went into relapse after this time point.

Conclusions

- The study found that 33.1% of adults diagnosed with asthma in the previous 5 years had no evidence of current asthma when they were evaluated with serial assessments of symptoms, lung function, and bronchial provocation tests while not using asthma medications.
- A large majority of participants (89%) in whom asthma was ruled out had asthma medications safely stopped for an additional 1-year period.
- Other considerations in reassessing asthma diagnosis include evaluating remission beyond symptoms and medication use, which may overlook subclinical active disease possibly associated with airway remodeling.
- Clinicians are encouraged to monitor and reassess asthma diagnoses in their asthma patients periodically, as this is a complex and dynamic disease that changes over time.

References: