Laurie Townsend, MD, MBA; Diane J. Madlon-Kay, MD, MS
University of Minnesota, Department of Family Medicine, Minneapolis

EDITOR
Anne Mounsey, MD
University of North Carolina Family Medicine Residency Program, Chapel Hill

Q/ Is it safe to add long-acting β-2 agonists to inhaled corticosteroids in patients with persistent asthma?

Evidence-Based Answer

A/ Possibly. Long-acting β-2 agonists (LABAs) used in combination with inhaled corticosteroids (ICS) don't appear to increase all-cause mortality or serious adverse events in patients with persistent asthma compared with ICS alone. Studies showing an increase in catastrophic events had serious methodologic issues. A large surveillance study is ongoing (strength of recommendation: **A**, meta-analysis of randomized controlled trials [RCTs]).

No significant difference in combination therapy vs ICS alone

In 2013, a Cochrane review analyzed the risk of mortality and nonfatal serious adverse events in patients treated with the LABA salmeterol in combination with ICS, compared with patients receiving the same dose of ICS alone.[1] The review included 35 RCTs of moderate quality with 13,447 adolescents and adults and 5 RCTs with 1862 children. Patients had all stages of asthma; mean study duration was 34 weeks in adult trials and 15 weeks in trials of children.

Seven deaths from all causes occurred in both the salmeterol-plus-ICS group and the ICS-alone group (35 trials, N=13,447; Peto odds ratio [OR]=0.90; 95% confidence interval [CI], 0.31-2.6). No deaths in children and no asthma-related deaths occurred in any study participants (40 trials, N=15,309).

Adults treated with ICS alone showed no significant difference from adults receiving combination therapy in the frequency of serious adverse events (defined as life threatening, requiring hospitalization or prolongation of existing hospitalization, or resulting in persistent or significant disability or incapacity). Adults on ICS had 21 events per 1000 compared with 24 per 1000 in adults on combination treatment (35 trials, N=13,447; Peto OR=1.2; 95% CI, 0.91-1.4).

Asthma-related serious adverse events were reported in 29 of 6986 adults in the combination group and 23 of 6461 in the ICS-alone group, a nonsignificant difference (35 trials, N=13,447; Peto OR=1.1; 95% CI, 0.65-1.9).

Only one serious asthma-related adverse event occurred in each group of children (ICS- and combination-treated); (5 trials, N=1862; Peto OR=0.99; 95% CI, 0.6-16). Because the number of events was so small and the results were so imprecise, a relative increase in all-cause mortality or nonfatal adverse events can't be completely ruled out.

Inconsistent dosages mar trials that show more catastrophic events

A systematic review of 7 RCTs with 7253 asthmatic patients compared LABA plus ICS or ICS alone at various doses. All of the trials included at least one catastrophic event, defined as an asthma-related intubation or death.[2] The mean ages of the patients varied from 11 to 48 years, and the length of the studies from 12 to 52 weeks. The risk of catastrophic events was greater in the LABA

plus ICS groups than ICS alone (OR=3.7; 95% CI, 1.4-9.6).

Only one of the 7 trials was included in the 2013 Cochrane review. The others were excluded because the control groups used different doses of ICS than the LABA-plus-ICS groups. In one trial, for example, the ICS group used 4 times the dose of budesonide used in the LABA-plus-ICS group. The difference in outcomes may therefore reflect the variation in ICS dose rather than the presence or absence of LABA.

Because of these conflicting results, the US Food and Drug Administration has mandated continued evaluation of LABAs by manufacturers.[3] Five clinical trials that are multinational, randomized, double-blind, and lasting at least 6 months will evaluate the safety of LABAs plus fixed-dose ICS compared with fixed-dose ICS alone. A total of 6200 children and 46,800 adults will be enrolled in the studies, whose results should be available in 2017. JFP

References

1. Cates CJ, Jaeschke R, Schmidt S, et al. Regular treatment with salmeterol and inhaled steroids for chronic asthma: serious adverse events. *Cochrane Database of Syst Rev.* 2013;(3):CD006922.
2. Salpeter SR, Wall AJ, Buckley NS. Long-acting beta-agonists with and without inhaled corticosteroids and catastrophic asthma events. *Am J Med.* 2010;123:322-328.
3. Chowdhury BA, Seymour SM, Levenson MS. Assessing the safety of adding LABAs to inhaled corticosteroids for treating asthma. *N Engl J Med.* 2011;364:2473-2475.

Q/ Do hormonal contraceptives lead to weight gain?

Maria Albright, MD; Saira Rani, MD; Thomas Gavagan, MD, MPH
University of Illinois at Chicago, College of Medicine

EDITOR
Corey Lyon, DO
University of Colorado Family Medicine Residency, Denver

Evidence-Based Answer

A/ It depends. Weight doesn't appear to increase with combined oral contraception (OC) compared with nonhormonal contraception, but percent body fat may increase slightly. Depot-medroxyprogesterone acetate injection (DMPA) users experience weight gain compared with OC and nonhormonal contraception (NH) users (strength of recommendation: **B**, cohort studies).

DMPA users gain more weight and body fat than OC users

A 2008 prospective, nonrandomized, controlled study of 703 women compared changes in weight, total fat, percent body fat, and central-to-peripheral fat ratio in 245 women using OC, 240 using DMPA, and 218 using NH methods of birth control.[1] Over the 36-month follow-up period, 257 women were lost to follow-up, 137 discontinued participation because they wanted a different contraceptive method, and 123 didn't complete the study for other reasons.

Compared to OC and NH users, DMPA users gained more actual weight (+5.1 kg) and body fat (+4.1 kg) and increased their percent body fat (+3.4%) and central-to-peripheral fat ratio (+0.1; $P<.01$ in all models). OC use wasn't associated with weight gain compared with the NH group but did increase OC users' percent body fat by 1.6% ($P<.01$) and decrease their total lean body mass by 0.36 ($P<.026$) (TABLE[1]).

DMPA users gain more weight in specific populations

For 18 months, researchers conducting a large prospective, nonrandomized study followed American adolescents ages 12 to 18 years who used DMPA and were classified as obese (defined as a baseline body mass index [BMI]