

# Combo Asthma Therapies May Deliver Same Control

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CHICAGO — Equivalent or better asthma control using combination therapy may be achieved with less budesonide/formoterol than with fluticasone/salmeterol in the first year of use, Samy Suissa, Ph.D., said at the annual meeting of the Ameri-

can College of Chest Physicians.

He and Dr. Pierre Ernst of McGill University Health Center, Montreal, reported an observational study in 23,075 patients, aged 4-95 years, with asthma, who were first-time users of budesonide/formoterol (6,918) or fluticasone/salmeterol (16,157). The therapies are the only combination treatments available in a single inhaler.

The investigators used the United Kingdom's General Research Database, which includes 6 million patients from about 450 practices, to identify patients who received their first budesonide/formoterol or fluticasone/salmeterol prescription from May 2001 (when both therapies became available in the United Kingdom) to December 2005.

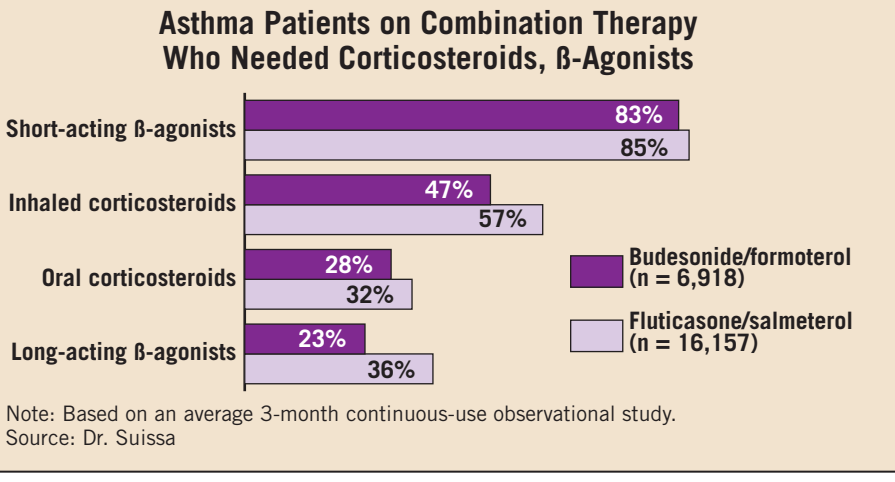
To emulate a prospective randomized trial, they conducted both intent-to-treat and persistent-treatment analyses on the frequency of prescriptions and health care events in the year after the first prescription. They adjusted for covariates measured during the year before this prescription.

A range of dosages and inhalers was used in each group. Patients with chronic obstructive pulmonary disease were excluded, said Dr. Suissa. He and Dr. Ernst have received research grants and speaker fees from, and have served on advisory boards for, AstraZeneca Pharmaceuticals LP, which manufactures budesonide/formoterol as Symbicort, and GlaxoSmithKline Inc., which makes fluticasone/salmeterol as Advair.

At baseline, budesonide/formoterol patients had a generally less severe asthma profile, compared with fluticasone/salmeterol patients, said Dr. Suissa, director of McGill's pharmacoepidemiology research unit, and professor of epidemiology, biostatistics, and medicine.

Budesonide/formoterol patients used fewer short-acting (83% vs. 85%) and long-acting (23% vs. 36%) β-agonists, and fewer oral (28% vs. 32%) and inhaled (47% vs. 57%) corticosteroids, and were less likely to have an asthma-related hospital visit (1% vs. 1.7%). Both groups saw a general provider an average of 10 times in the year before their combination therapy prescription. The mean ages were 44 years (budesonide/formoterol) and 43 years (fluticasone/salmeterol). In the intent-to-treat analysis, budesonide/formoterol patients received 14% fewer prescriptions for their study drug than did fluticasone/salmeterol patients, 8% fewer prescriptions for other asthma medications, and 9% fewer antibiotic prescriptions.

Persistent treatment (two prescriptions with a gap of less than 7 days between them), averaged 3.1 months in the budesonide/formoterol group and 2.8 months in the fluticasone/salmeterol group. After adjustment for baseline determinants, duration of persistent use was 15% longer for budesonide/formoterol patients. In the persistent-treatment analysis, which covered only the 3 months on average of continuous use, budesonide/formoterol patients got 11% fewer prescriptions for their therapy than did fluticasone/salmeterol patients, 8% fewer prescriptions for other asthma medications, and 11% fewer antibiotic prescriptions. ■



Before prescribing, please consult Full Prescribing Information.

**INDICATIONS AND USAGE**  
CHANTIX is indicated as an aid to smoking cessation treatment.

**PRECAUTIONS**  
**General** Nausea was the most common adverse event associated with CHANTIX treatment. Nausea was generally described as mild or moderate and often transient; however, for some subjects, it was persistent over several months. The incidence of nausea was dose-dependent. Initial dose-titration was beneficial in reducing the occurrence of nausea. Nausea was reported by approximately 30% of patients treated with CHANTIX 1 mg BID after an initial week of dose titration. In patients taking CHANTIX 0.5 mg BID, the incidence of nausea was 16% following initial titration. Approximately 3% of subjects treated with CHANTIX 1 mg BID in studies involving 12 weeks of treatment discontinued treatment prematurely because of nausea. For patients with intolerable nausea, dose reduction should be considered.

**Effect of smoking cessation:** Physiological changes resulting from smoking cessation, with or without treatment with CHANTIX, may alter the pharmacokinetics or pharmacodynamics of some drugs, for which dosage adjustment may be necessary (examples include theophylline, warfarin and insulin).

**Drug Interactions** Based on varenicline characteristics and clinical experience to date, CHANTIX has no clinically meaningful pharmacokinetic drug interactions (See Full Prescribing Information, CLINICAL PHARMACOLOGY, Drug-Drug Interactions).

**Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenesis. Lifetime carcinogenicity studies were performed in CD-1 mice and Sprague-Dawley rats. There was no evidence of a carcinogenic effect in mice administered varenicline by oral gavage for 2 years at doses up to 20 mg/kg/day (47 times the maximum recommended human daily exposure based on AUC). Rats were administered varenicline (1, 5, and 15 mg/kg/day) by oral gavage for 2 years. In male rats (n = 65 per sex per dose group), incidences of fibrosarcoma (tumor of the brown fat) were increased at the mid dose (1 tumor, 5 mg/kg/day, 23 times the maximum recommended human daily exposure based on AUC) and maximum dose (2 tumors, 15 mg/kg/day, 67 times the maximum recommended human daily exposure based on AUC). The clinical relevance of this finding to humans has not been established. There was no evidence of carcinogenicity in female rats.

Mutagenesis. Varenicline was not genotoxic, with or without metabolic activation, in the following assays: Ames bacterial mutation assay; mammalian CHO/HGPRT assay; and tests for cytogenetic aberrations *in vivo* in rat bone marrow and *in vitro* in human lymphocytes.

Impairment of fertility. There was no evidence of impairment of fertility in either male or female Sprague-Dawley rats administered varenicline succinate up to 15 mg/kg/day (67 and 36 times, respectively, the maximum recommended human daily exposure based on AUC at 1 mg BID). However, a decrease in fertility was noted in the offspring of pregnant rats who were administered varenicline succinate at an oral dose of 15 mg/kg/day (36 times the maximum recommended human daily exposure based on AUC at 1 mg BID). This decrease in fertility in the offspring of treated female rats was not evident at an oral dose of 3 mg/kg/day (9 times the maximum recommended human daily exposure based on AUC at 1 mg BID).

**Pregnancy** Pregnancy Category C. Varenicline succinate was not teratogenic in rats and rabbits at oral doses up to 15 and 30 mg/kg/day, respectively (36 and 50-times the maximum recommended human daily exposure based on AUC at 1 mg BID, respectively). Nonteratogenic effects Varenicline succinate has been shown to have an adverse effect on the fetus in animal reproduction studies. Administration of varenicline succinate to pregnant rabbits resulted in reduced fetal weights at an oral dose of 30 mg/kg/day (50 times the human AUC at 1 mg BID); this reduction was not evident following treatment with 10 mg/kg/day (23 times the maximum recommended human exposure based on AUC). In addition, in the offspring of pregnant rats treated with varenicline succinate there were decreases in fertility and increases in auditory startle response at an oral dose of 15 mg/kg/day (36 times the maximum recommended human daily exposure based on AUC). There are no adequate and well-controlled studies in pregnant women. CHANTIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing mothers** Although it is not known whether this drug is excreted in human milk, animal studies have demonstrated that varenicline can be transferred to nursing pups. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CHANTIX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Labor and delivery** The potential effects of CHANTIX on labor and delivery are not known. **Pediatric Use** Safety and effectiveness of CHANTIX in pediatric patients have not been established; therefore, CHANTIX is not recommended for use in patients under 18 years of age. **Geriatric Use** A combined single and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1 mg varenicline given QD or BID to 16 healthy elderly male and female smokers (aged 65-75 yrs) for 7 consecutive days was similar to that of younger subjects. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Varenicline is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see **DOSE AND ADMINISTRATION, Special Populations, Patients with impaired renal function**). No dosage adjustment is recommended for elderly patients (see **DOSE AND ADMINISTRATION, Special Populations**).

(Table 3 continued)

PSYCHIATRIC DISORDERS			
Sleep Disorders/Disturbances			
Insomnia**	19	18	13
Abnormal dreams	9	13	5
Sleep disorder	2	5	3
Nightmare	2	1	0
NERVOUS SYSTEM			
Headaches			
Headache	19	15	13
Neurological Disorders NEC			
Dysgeusia	8	5	4
Somnolence	3	3	2
Lethargy	2	1	0
GENERAL DISORDERS			
General Disorders NEC			
Fatigue/Malaise/Asthenia	4	7	6
RESPIRATORY/MEDIAST			
Respiratory Disorders NEC			
Rhinorrhea	0	1	0
Dyspnea	2	1	1
Upper Respiratory Tract Disorder	7	5	4
SKIN/SUBCUTANEOUS TISSUE			
Epidermal and Dermal Conditions			
Rash	1	3	2
Pruritus	0	1	1
METABOLISM & NUTRITION			
Appetite/General Nutr. Disorders			
Increased appetite	4	3	2
Decreased appetite/Anorexia		2	1

\* Includes PTs Abdominal (pain, pain upper, pain lower, discomfort, tenderness, distension) and Stomach discomfort  
\*\* Includes PTs Insomnia/Initial insomnia/Middle insomnia/Early morning awakening

The overall pattern, and the frequency of adverse events during the longer-term trials was very similar to that described in Table 3, though several of the most common events were reported by a greater proportion of patients. Nausea, for instance, was reported in 40% of patients treated with CHANTIX 1 mg BID in a one-year study, compared to 8% of placebo-treated patients.

Following is a list of treatment-emergent adverse events reported by patients treated with CHANTIX during all clinical trials. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening. **BLOOD AND LYMPHATIC SYSTEM DISORDERS:** Infrequent: Anemia, Lymphadenopathy. **Rare:** Leukocytosis, Thrombocytopenia, Splenomegaly. **CARDIAC DISORDERS:** Infrequent: Angina pectoris, Arrhythmia, Bradycardia, Ventricular extrasystoles, Myocardial infarction, Palpitations, Tachycardia. **Rare:** Atrial fibrillation, Cardiac flutter, Coronary artery disease, Cor pulmonale, Acute coronary syndrome. **EAR AND LABYRINTH DISORDERS:** Infrequent: Tinnitus, Vertigo. **Rare:** Deafness, Meniere's disease. **ENDOCRINE DISORDERS:** Infrequent: Thyroid gland disorders. **EYE DISORDERS:** Infrequent: Conjunctivitis, Dry eye, Eye irritation, Vision blurred, Visual disturbance, Eye pain. **Rare:** Acquired night blindness, Blindness transient, Cataract subcapsular, Ocular vascular disorder, Photophobia, Vitreous floaters. **GASTROINTESTINAL DISORDERS:** Frequent: Diarrhea, Gingivitis. **Infrequent:** Dysphagia, Enterocolitis, Eructation, Gastritis, Gastrointestinal hemorrhage, Mouth ulceration, Esophagitis. **Rare:** Gastric ulcer, Intestinal obstruction, Pancreatitis acute. **GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS:** Frequent: Chest pain, influenza like illness, Edema, Thirst. **Infrequent:** Chest discomfort, Chills, Pyrexia. **HEPATOBIILIARY DISORDERS:** Infrequent: Gall bladder disorder. **IMMUNE SYSTEM DISORDERS:** Infrequent: Hypersensitivity. **Rare:** Drug hypersensitivity. **INVESTIGATIONS:** Frequent: Liver function test abnormal. Weight increased. **Infrequent:** Electrocardiogram abnormal, Muscle enzyme increased, Urine analysis abnormal. **METABOLISM AND NUTRITION DISORDERS:** Infrequent: Diabetes mellitus, Hyperlipidemia, Hypokalemia. **Rare:** Hyperkalemia, Hypoglycemia. **MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS:** Frequent: Arthralgia, Back pain, Muscle cramp, Musculoskeletal pain, Myalgia. **Infrequent:** Arthritis, Osteoporosis. **Rare:** Myositis. **NERVOUS SYSTEM DISORDERS:** Frequent: Disturbance in attention, Dizziness, Sensory disturbance. **Infrequent:** Amnesia, Migraine, Parosmia, Psychomotor hyperactivity, Restless legs syndrome, Syncope, Tremor. **Rare:** Balance disorder, Cerebrovascular accident, Convulsion, Dysarthria, Facial palsy, Mental impairment, Multiple sclerosis, Nystagmus, Psychomotor skills impaired, Transient ischemic attack, Visual field defect. **PSYCHIATRIC DISORDERS:** Frequent: Anxiety, Depression, Emotional distress, Irritability, Restlessness. **Infrequent:** Aggression, Agitation, Disorientation, Dissociation, Libido decreased, Mood swings, Thinking abnormal. **Rare:** Bradyphrenia, Euphoric mood, Hallucination, Psychotic disorder, Suicidal ideation. **RENAL AND URINARY DISORDERS:** Frequent: Polyuria. **Infrequent:** Nephrothiasis, Nocturia, Urine abnormality, Urinary syndrome. **Rare:** Renal failure acute, Urinary retention. **REPRODUCTIVE SYSTEM AND BREAD DISORDERS:** Frequent: Menstrual disorder. **Infrequent:** Erectile dysfunction. **Rare:** Sexual dysfunction. **RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS:** Frequent: Epistaxis, Respiratory disorders. **Infrequent:** Asthma. **Rare:** Pleurisy, Pulmonary embolism. **SKIN AND SUBCUTANEOUS TISSUE DISORDERS:** Frequent: Hyperhidrosis. **Infrequent:** Acne, Dermatitis, Dry skin, Eczema, Erythema, Psoriasis, Urticaria. **Rare:** Photosensitivity reaction. **VASCULAR DISORDERS:** Frequent: Hot flush, Hypertension. **Infrequent:** Hypotension, Peripheral ischemia, Thrombosis.

**DRUG ABUSE AND DEPENDENCE**  
**Controlled Substance Class** Varenicline is not a controlled substance. **Humans:** Fewer than 1 out of 1000 patients reported euphoria in clinical trials with CHANTIX. At higher doses (greater than 2 mg), CHANTIX produced more frequent reports of gastrointestinal disturbances such as nausea and vomiting. There is no evidence of dose-escalation to maintain therapeutic effects in clinical studies, which suggests that tolerance does not develop. Abrupt discontinuation of CHANTIX was associated with an increase in irritability and sleep disturbances in up to 3% of patients. This suggests that, in some patients, varenicline may produce mild physical dependence which is not associated with addiction. In a human laboratory abuse liability study, a single oral dose of 1 mg varenicline did not produce any significant positive or negative subjective responses in smokers. In non-smokers, 1 mg varenicline produced an increase in some positive subjective effects, but this was accompanied by an increase in negative adverse effects, especially nausea. A single oral dose of 3 mg varenicline uniformly produced unpleasant subjective responses in both smokers and non-smokers. **Animals:** Studies in rodents have shown that varenicline produces behavioral responses similar to those produced by nicotine. In rats trained to discriminate nicotine from saline, varenicline produced full generalization to the nicotine cue. In self-administration studies, the degree to which varenicline substitutes for nicotine is dependent upon the requirement of the task. Rats trained to self-administer nicotine under easy conditions continued to self-administer varenicline to a degree comparable to that of nicotine, however in a more demanding task, rats self-administered varenicline to a lesser extent than nicotine. Varenicline pretreatment also reduced nicotine self-administration.

**OVERDOSEAGE**  
In case of overdose, standard supportive measures should be instituted as required. Varenicline has been shown to be dialyzed in patients with end stage renal disease (see Full Prescribing Information, CLINICAL PHARMACOLOGY, Pharmacokinetics, Pharmacokinetics in Special Patient Populations), however, there is no experience in dialysis following overdose.

**DOSE AND ADMINISTRATION**  
**Usual Dosage for Adults** Smoking cessation therapies are more likely to succeed for patients who are motivated to stop smoking and who are provided additional advice and support. Patients should be provided with appropriate educational materials and counseling to support the quit attempt. The patient should set a date to stop smoking. CHANTIX dosing should start one week before this date. CHANTIX should be taken after eating and with a full glass of water. The recommended dose of CHANTIX is 1 mg twice daily following a 1-week titration as follows:

Days 1–3:	0.5 mg once daily
Days 4–7:	0.5 mg twice daily
Days 8–End of treatment:	1 mg twice daily

Patients who cannot tolerate adverse effects of CHANTIX may have the dose lowered temporarily or permanently. Patients should be treated with CHANTIX for 12 weeks. For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment with CHANTIX is recommended to further increase the likelihood of long-term abstinence. Patients who do not succeed in stopping smoking during 12 weeks of initial therapy, or who relapse after treatment, should be encouraged to make another attempt once factors contributing to the failed attempt have been identified and addressed.

**Special Populations**

**Patients with impaired renal function** No dosage adjustment is necessary for patients with mild to moderate renal impairment. For patients with severe renal impairment, the recommended starting dose of CHANTIX is 0.5 mg once daily. Patients may then titrate as needed to a maximum dose of 0.5 mg twice a day. For patients with end-stage renal disease undergoing hemodialysis, a maximum dose of 0.5 mg once daily may be administered if tolerated well (See Full Prescribing Information, CLINICAL PHARMACOLOGY, Pharmacokinetics, Pharmacokinetics in Special Populations, Renal impairment).

**Dosing in elderly patients and patients with impaired hepatic function** No dosage adjustment is necessary for patients with hepatic impairment. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (See **PRECAUTIONS, Geriatric Use**).

**Use in children** Safety and effectiveness of CHANTIX in pediatric patients have not been established; therefore, CHANTIX is not recommended for use in patients under 18 years of age.

Rx only

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