allocated across a population. Accordingly, a major focus of public health ethics is maximizing the health of the population while minimizing infringements on individual liberty.[2] Ethical dilemmas arising from the tension between the two are typically posed by cases in which a person refuses to comply with a public health imperative (such as mandatory vaccination or quarantine). Less common are cases in which a person demands an intervention that is perceived as conferring individual benefit but that might contribute to net harm to the public health. The personal stockpiling of oseltamivir for a potential avian influenza pandemic represents just such a case.

The current supply of oseltamivir is inadequate to meet the demand that would arise in the event of an avian influenza pandemic. Moreover, personal stockpiling of oseltamivir depletes the supply available for patients who could benefit from the drug during the usual human influenza season: a person who is assertive enough to ask for a prescription does not necessarily need the drug more than unassertive people do. The likely confusion about whether to use stockpiled oseltamivir for prophylaxis or treatment and the probability that much will be used for illnesses other than influenza are relevant from the public health perspective as well. Finally, the inappropriate or chaotic use of oseltamivir will increase the risk that resistant strains of influenza virus will develop. These considerations strongly suggest that random stockpiling of oseltamivir would confer no benefit to the overall population and would probably confer harm.

Thus, an individual physician has no obligation to prescribe oseltamivir in response to a patient's request — a position that discourages prescribing of the drug but does not prohibit it. In contrast, the public health perspective clearly suggests that the physician has an obligation not to prescribe oseltamivir — a position that is tantamount to a prohibition against prescribing it. The public health perspective need not always trump the individual perspective, but since both point in the same direction in this instance, the prohibition should prevail.

As in 2001, when physicians were besieged with demands for ciprofloxacin after the anthrax attacks, this year's run on oseltamivir should stimulate public health experts to consider more generally the dilemma encountered by physicians who have simultaneous obligations to individual patients and to public health. Physicians who faced demands for oseltamivir in the early fall of 2005 would have welcomed explicit directives from public health institutions such as the Centers for Disease Control and Prevention and state departments of health. Such directives were helpful in the fall of 2004 when physicians were forced to ration influenza vaccine.[3] In the absence of formal guidelines from the government, some professional societies[4] and private medical groups[5] have stepped in to issue statements that are consistent with our conclusion: physicians should decline any request for a prescription for the purpose of stockpiling oseltamivir, optimally with an explanation that reflects the reasoning here.

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Safety of Long-Acting Beta-Agonists — An Urgent Need to Clear the Air

Fernando D. Martinez, M.D.

Eleven years after the first long-acting beta-agonist, salmeterol, was approved for sale in the United States, the Food and Drug Administration (FDA) has issued a stern public health advisory alerting "health care professionals and patients that these medicines may increase the chance of severe asthma episodes, and death when those episodes occur" (www.fda.gov/cder/drug/advisory/LABA.htm). The announcement followed a July 2005 meeting of an FDA advisory committee on this topic. What are the

consequences of this advisory for the treatment of asthma?

Currently, inhaled corticosteroids are the most effective treatment for the symptoms of persistent asthma. However, in patients with severe disease, these drugs often fail to control asthma symptoms fully, necessitating additional treatment with inhaled bronchodilators. Until the early 1990s, the only effective inhaled bronchodilators available were short-acting beta$_2$-adrenergic agonists such as albuterol. Since these agents have a duration of action of four to six hours, patients whose asthma symptoms were not controlled by inhaled corticosteroids needed to use them several times a day to obtain continuous relief.

To decrease the treatment burden, inhaled beta-agonists with a duration of action of 10 to 16 hours were developed. These long-acting beta-agonists, which include salmeterol and formoterol, were shown to be effective in improving symptom control and lung function for 12 hours or more when added to inhaled corticosteroid therapy.[1]

However, after long-acting beta-agonists were introduced outside the United States, concern about increased rates of severe illness and asthma-related death associated with these agents prompted researchers in the United Kingdom to undertake a large randomized, double-blind study comparing salmeterol with albuterol (salbutamol) as daily therapy supplementing the usual treatment for asthma; the study enrolled more than 25,000 patients and lasted 16 weeks.[2] Patients receiving salmeterol were three times as likely to die from asthma during the trial as those treated with albuterol (12 of 16,787 patients vs. 2 of 8393 patients). Since these events were so rare, the results were not statistically significant ($P=0.10$). Nevertheless, there was one death attributable to salmeterol for every 650 patient-years of treatment.

But interpretation of these results was not straightforward. The study was not designed to test the hypothesis that salmeterol would increase the risk of death regardless of concomitant treatment with inhaled corticosteroids. Moreover, bias may have been introduced by the withdrawal from the study of a higher proportion of patients in the albuterol group than in the salmeterol group. Given the uncertainty, the FDA asked GlaxoSmithKline, the manufacturer of salmeterol (sold in the United States as Serevent or, in combination with the inhaled steroid fluticasone, as Advair), to obtain additional data. This request led to the Salmeterol Multicenter Asthma Research Trial (SMART), in which patients with asthma were randomly assigned to receive either salmeterol or placebo for 28 weeks in addition to their usual therapy. Inexplicably, SMART, like the United Kingdom study, was not designed to test the hypothesis that salmeterol was safe to use as an adjunct to inhaled corticosteroids: subjects underwent randomization without consideration of their current corticosteroid therapy, and no records of such therapy were kept during the trial.

An interim analysis, performed after approximately 26,000 patients had been enrolled, showed that asthma-related death was 4.4 times as likely in the salmeterol group as in the placebo group (95 percent confidence interval, 1.3 to 15.3; $P=0.02$). Similar numbers of subjects in the two groups withdrew from the study. One death was attributable to salmeterol for every 700 patient-years of treatment, a result strikingly similar to that in the United Kingdom study. At this point, the manufacturer halted the study.

No studies similar to SMART are available for formoterol, a long-acting beta-agonist that Novartis markets in the United States under the name Foradil. However, tabular data that Novartis provided for the FDA advisory committee (see table)[3] showed an increased incidence of serious asthma-related events in patients taking formoterol — a trend found among both patients who were using inhaled corticosteroids concomitantly and those who were not.

In responding to these findings, the manufacturers have argued that a case–control study recently performed in the United Kingdom showed no increased prescription of long-acting beta-agonists among patients who died with a diagnosis of asthma, as compared with control patients who were matched according to age and the date of an index hospitalization for asthma.[4] However, patients included in that study were considerably older than those enrolled in SMART; the ascertainment of the prescription of long-acting beta-agonists was retrospective, and patients could have started or stopped their use without its being recorded; and the results could have been biased by the fact that 42 percent of the patients had a concomitant diagnosis of chronic obstructive pulmonary disease, a condition in which severe adverse reactions to these drugs do not seem to occur. The manufacturers have also argued that asthma-related mortality has not increased since long-acting beta-agonists were first introduced: if anything, it has de-

Asthma-Related Serious Adverse Events with Formoterol, as Compared with Placebo or Albuterol.*

Group	Formoterol			Placebo	Albuterol
	any dose	*20–24 μg/day*	*48 μg/day*		
All patients					
No. of patients	3768	1948	1156	1863	630
No. of adverse events	43	18	22	5	4
Rate per 100 patient-yr of treatment	3.9	3.5	5.6	0.9	3.1
Patients using inhaled corticosteroids					
No. of patients	2488	1389	685	1319	427
No. of adverse events	26	13	12	4	4
Rate per 100 patient-yr of treatment	3.3	3.0	4.8	1.0	4.3
Patients not using inhaled corticosteroids					
No. of patients	1280	559	471	544	203
No. of adverse events	17	5	10	1	0
Rate per 100 patient-yr of treatment	5.2	4.8	6.8	0.6	0

* Data are from Novartis and include placebo-controlled clinical trials of at least four weeks in duration. Twenty-four micrograms of formoterol per day is the dose currently approved in the United States; albuterol was taken four times daily, according to a regular schedule.

creased.[5] There is no clear explanation for this apparent discrepancy, but successful efforts to promote inhaled corticosteroids as the primary medicine for controlling asthma may have contributed to a decrease in mortality that masked an increase associated with long-acting beta-agonists.

Taken together, the evidence indicates that regular treatment with long-acting beta-agonists is associated with increased risks of severe exacerbations of asthma and of death from asthma in a small but not inconsequential subgroup of patients. Unfortunately, the limitations of the trials conducted to date preclude definitive conclusions regarding the potential for inhaled corticosteroids to limit or prevent these adverse outcomes.

How do we reconcile in clinical practice the established beneficial effects of long-acting beta-agonists on asthma control with their rare potential for contributing to severe illness or death? In patients with mild-to-moderate asthma, inhaled corticosteroids should be used in sufficient amounts to control chronic symptoms. If symptoms cannot be controlled in this way, some such patients may also benefit from the addition of leukotriene-receptor antagonists or low-dose theophylline therapy. With adequate doses of inhaled corticosteroids and other treatments, long-acting beta-agonists should not usually be needed.

For patients with more severe disease, who still require two or more daily administrations of albuterol in addition to adequate doses of inhaled corticosteroids, thorough patient characterization should precede any additional therapeutic intervention. Data show that symptoms in one third to one half of these patients may be explained by nonadherence to therapy or the coexistence of other conditions that are not responsive to beta-agonists. Once such conditions have been ruled out, long-acting beta-agonists may be added to inhaled corticosteroid therapy to relieve symptoms. Since we still do not know whether long-acting beta-agonists pose a risk when used appropriately in such patients, close medical monitoring is necessary, and users should be cautioned to continue taking all their asthma medications and to seek medical care should their symptoms remain uncontrolled or worsen despite this dual treatment. Until the manufacturers of these drugs undertake the appropriate studies needed to clear the air, the safety of long-acting beta-agonists will remain uncertain.

Dr. Martinez reports having received consulting and lecture fees from Genentech, Pfizer, and Merck. He served on the FDA Advisory Committee that met in July 2005 regarding long-acting beta-agonists.

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