A Randomized Controlled Noninferiority Trial of Single Dose of Oral Dexamethasone Versus 5 Days of Oral Prednisone in Acute Adult Asthma

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Study objective: Oral dexamethasone demonstrates bioavailability similar to that of oral prednisone but has a longer half-life. We evaluate whether a single dose of oral dexamethasone plus 4 days of placebo is not inferior to 5 days of oral prednisone in treatment of adults with mild to moderate asthma exacerbations to prevent relapse defined as an unscheduled return visit for additional treatment for persistent or worsening asthma within 14 days.

Methods: Adult emergency department patients (aged 18 to 55 years) were randomized to receive either a single dose of 12 mg of oral dexamethasone with 4 days of placebo or a 5-day course of oral prednisone 60 mg a day. Outcomes including relapse were assessed by a follow-up telephone interview at 2 weeks.

Results: One hundred seventy-three dexamethasone and 203 prednisone subjects completed the study regimen and telephone follow-up. The dexamethasone group by a small margin surpassed the preset 8% difference between groups for noninferiority in relapse rates within 14 days (12.1% versus 9.8%; difference 2.3%; 95% confidence interval −4.1% to 8.6%). Subjects in the 2 groups had similar rates of hospitalization for their relapse visit (dexamethasone 3.4% versus prednisone 2.9%; difference 0.5%; 95% confidence interval −4.1% to 3.1%). Adverse effect rates were generally the same in the 2 groups.

Conclusion: A single dose of oral dexamethasone did not demonstrate noninferiority to prednisone for 5 days by a very small margin for treatment of adults with mild to moderate asthma exacerbations. Enhanced compliance and convenience may support the use of dexamethasone regardless. [Ann Emerg Med. 2016;■:1-6.]

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INTRODUCTION

Background

Asthma accounts for more than 2.1 million unscheduled emergency department (ED) visits annually, with a prevalence that includes 8.4% of the population.[1] Systemic corticosteroids serve as a cornerstone of acute asthma therapy. Relapse rate, length of stay, and hospitalization rates decline with the routine use of steroids.[2] Intravenous, intramuscular, and oral preparations demonstrate equivalence in clinical studies.[3-5] Guidelines from the National Heart, Lung, and Blood Institute recommend early oral corticosteroids to treat moderate to severe asthma exacerbations or mild exacerbations with no immediate and complete response to β-agonist therapy and suggest a minimum length of treatment of 5 days of oral prednisone.[6]

Importance

Oral dexamethasone exhibits bioavailability similar to that of intramuscular and intravenous dexamethasone, with a duration of action up to 72 hours.[7-10] Dexamethasone for acute asthma treatment emerged initially in the pediatric literature, with promising results.[11-13] Kravitz et al[14] evaluated a 2-dose regimen of oral dexamethasone in adults, demonstrating a statistically significant increase in return to normal activities in 3 days. Because there is a strong association between low adherence and poor outcomes,[15,16] we posited that reducing the role of patient adherence to the care plan would improve outcomes. A single dose of a long-acting oral medication administered in the ED might achieve such a goal.

Goals of This Investigation

The objective of this study is to evaluate whether a single dose of oral dexamethasone plus 4 days of placebo is not inferior to 5 days of oral prednisone in the treatment of adults with mild to moderate asthma exacerbations to prevent relapse, which we define as an unscheduled return visit to a health care provider for additional treatment for persistent or worsening asthma within 14 days.

Editor's Capsule Summary

What is already known on this topic

Single oral doses of longer-acting corticosteroids might be just as effective as multi-day short courses of prednisone.

What question this study addressed

For adults with mild to moderate exacerbations of asthma, is a single oral dose of dexamethasone 12 mg inferior to prednisone 60 mg daily for 5 days?

What this study adds to our knowledge

In this randomized, double-blind trial of 376 patients, the frequency of relapse within 14 days trended slightly higher with dexamethasone (12.1% versus 9.8%). While this 2.3% difference was smaller than the 8% difference the authors considered clinically important, its confidence interval extended above 8% so, technically, this study does not unequivocally establish similarity.

How this is relevant to clinical practice

A single dose of oral dexamethasone 12 mg is either similar to or slightly inferior to a 5-day course of prednisone 60 mg for asthma.

MATERIALS AND METHODS

Study Design and Setting

This was a prospective, randomized, triple-blind, controlled study conducted between 2011 and 2015 in the urban ED of Highland Hospital in Oakland, CA, a training institution with an annual ED census of 90,000 patient visits per year. The Alameda Health System institutional review board approved the study. This trial is reported in accordance with Consolidated Standards of Reporting Trials standards.

Selection of Participants

The ED respiratory therapist, who is available 24 hours a day and 7 days a week, identified and screened patients for eligibility when the first nebulizer treatment was initiated. In our ED, only the respiratory therapist administers nebulizers, and thus their screening captures all patients who potentially meet the inclusion criteria. Patients were eligible for inclusion in the study if they were aged 18 to 55 years, had a history of asthma, presented to the ED with an acute episode of asthma requiring more than 1 albuterol nebulizer treatment, and were discharged home with a valid telephone number for follow-up.

We excluded from the study patients who were younger than 18 years or older than 55 years. The age limit of 55 years was an attempt to limit inadvertent enrollment of patients who also have concurrent chronic obstructive pulmonary disease. We also excluded patients without a working telephone number because the follow-up was by telephone, who were pregnant, who had previous allergic reaction to corticosteroids, who reported use of oral corticosteroids 2 weeks before presentation, or who had a history of a chronic respiratory disease such as chronic obstructive pulmonary disease or pulmonary fibrosis, HIV/AIDS, congestive heart failure, active varicella, active tuberculosis, or diabetes mellitus. We excluded patients with severe asthma requiring immediate airway intervention such as noninvasive bilevel airway support or intubation and those who were admitted to the hospital. In our customary ED work flow, admission decisions occur well after steroid administration, so we excluded this last group, hospital admissions, after randomization.

Interventions

Once patients met initial enrollment criteria with informed consent, the treating provider placed an electronic order for the study medication to officially enroll the patient in the study. Treating providers ordered nebulizer treatments at their discretion without a study protocol. Once the electronic study medication order was placed, a randomization table maintained by the pharmacy assigned subjects to one of the 2 treatment arms. Subjects in the prednisone group received the first dose of a single capsule of prednisone 60 mg in the ED and were discharged with a bottle containing 4 additional capsules of prednisone 60 mg to be received once per day for a total of 5 days. Subjects in the dexamethasone group received a single dose of a single capsule of dexamethasone 12 mg in the ED and were discharged with a bottle containing 4 additional capsules of placebo to be received once per day for a total of 5 days. The capsules were identical and prepared by Advantage Pharmaceuticals, which was otherwise not involved in the trial. Because the capsules were identical, the treating provider, nurse, pharmacist, and study participant were unable to discern the medication administered. Individuals responsible for collection, tabulation, and analysis of the data were also blinded to treatment allocation until data analysis was completed. We confirmed administration of the study medication by a review of the electronic medical record, as well as confirmation by the study participant during the telephone follow-up.

Methods of Measurement

Using a standardized and pilot-tested data collection form, trained respiratory therapists consecutively enrolled

subjects without the necessity of a study investigator's presence and collected baseline data, including age, sex, height, race, home asthma medications (including whether the patient exhausted the medication supply), duration of symptoms, and asthma history (including past intubations, hospitalization, recent ED visits in last 4 weeks, and smoking). The data form also included initial and discharge vital signs (pulse rate, respiratory rate, and oxygen saturation), along with peak expiratory flow rates, total treatments of nebulized medications, and discharge medications prescribed. If there were any missing or spurious measurements, the research assistant reviewed the electronic medical record from the visit to determine the appropriate value. Two authors (MWR and HA) adjudicated any discrepancies.

Trained research staff, blind to allocation group, contacted study participants by telephone 2 weeks after the index ED visit to complete a follow-up survey in Spanish or English. The survey included the primary outcome, whether they had consulted a physician in the last 14 days after visiting the ED, and, if so, whether it was a follow-up or routine visit or an emergency visit for worsening asthma. Research staff also asked study participants about adverse effects, current symptoms, and current required asthma treatment.

Outcome Measures

We chose as our primary outcome measure relapse, defined as an unscheduled return visit to a health care provider for additional treatment for persistent or worsening asthma within 14 days. We selected relapse over other options, in particular severity scores, because it has been used as a primary outcome in previous related studies, including the most recent Cochrane review on this topic.[2,13,17] Moreover, there is a lack of consensus for a core severity scoring system because of each instrument's limitations.[18] Secondary outcomes focused on adverse effects and current asthma symptoms.

Primary Data Analysis

We powered the study as a noninferiority trial to show that a single dose of dexamethasone plus placebo was not inferior to a pulse dose of prednisone. The analytic plan used a relapse rate of 16%, based on historical analysis of the hospital electronic database from the previous 2 years, which was similar to national relapse rates.[19] Initially, we calculated the sample size of 520 for a noninferiority trial, with a 16% relapse rate at 80% power, α=.05, and an 8% difference between groups, with a plan to adjust the sample size after an interim analysis. The choice of 8% threshold results from the difference of the placebo (33%) and historic relapse rates (16%) to detect 50% superiority to placebo rates.[20,21] The interim analysis near enrollment of 200 subjects demonstrated an 11% overall relapse rate. We adjusted the sample size for the 11% relapse rate for a new sample size of 375 to limit the upper bound of the 95% confidence interval (CI) on the unchanged difference between the groups of 8%.[22]

Our data analysis team was blinded to allocation arm, coding the analytic plan to group A and group B, until the results were final and the blind was lifted in the article-writing phase. We performed descriptive statistics with standard analytics based on intention-to-treat principles, reporting 95% CIs when appropriate. We performed all analyses with Stata (version 11.2; StataCorp, College Station, TX).

RESULTS

Characteristics of Study Subjects

A total of 376 subjects were analyzable in this study. A patient flow diagram is shown in the Figure.

The prednisone and dexamethasone groups showed well-balanced baseline characteristics, including age, sex, race or ethnicity, asthma severity history, home inhaled steroid use, vital signs, peak flow rates, and ED-based treatments (Table 1).

Main Results

Our primary outcome, relapse as defined by return visit for asthma within 14 days, occurred among 12.1% of the dexamethasone group and 9.8% of prednisone controls, for a difference of 2.3% between groups. The 95% confidence limits on the difference (–4.1% to 8.6%) fell just outside our prespecified noninferiority threshold of 8%. Subjects in the 2 groups demonstrated similar rates of hospitalization in the event of a relapse and similar rates of subjective improvement in symptoms. Adverse effect rates did not appear to differ substantially between the 2 groups, except for abdominal pain, which predominated in the prednisone group (Table 2).

Given the imbalance in our cohort of loss to follow-up, we performed 2 "worst-case" sensitivity analyses to assess the robustness of the result. In sensitivity analysis 1, we allocated all subjects in the dexamethasone group who were lost to treatment failure and all those lost in the prednisone group to success. In this scenario, the relapse rate for dexamethasone was 29% compared with 8.4% for prednisone, for a difference favoring prednisone of 20% (95% CI 13% to 27%). In contrast, sensitivity analysis 2 imagines that all subjects lost to the dexamethasone group

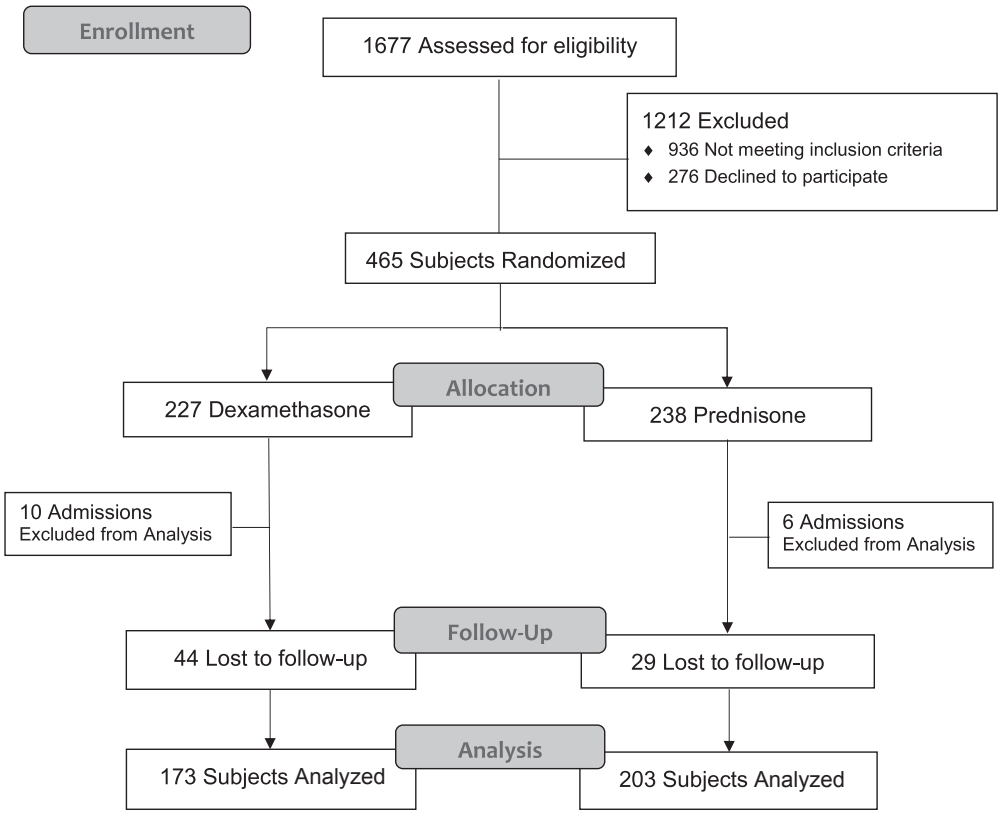

Figure. Patient enrollment, allocation, follow-up, and analysis.

were event free, whereas all the prednisone subjects lost experienced a relapse. In the second scenario, the relapse rate for dexamethasone was 13% compared with 23% for prednisone, for a difference favoring dexamethasone of 10% (95% CI 7.3% to 20%).

LIMITATIONS

First, the patients lost to follow-up potentially limited the study. Our rate of loss to follow-up of approximately 20% is similar to that in the study by Kravitz et al[14] (22%) and to that of study populations in safety-net hospitals in general. Yet even in a worst-case scenario, we estimate the difference in relapse to be 20%, similar to previous worst-case scenario estimates in asthma trials.

Second, the primary and secondary outcomes based on a telephone follow-up survey potentially limited the study. The survey follow-up required a study participant to remember the last 2 weeks and any unscheduled visits for worsening asthma and may have been vulnerable to recall bias. The survey also limited the assessment of the subject's current condition without a physical examination.

Third, despite attempts in the exclusion criteria, the study potentially included subjects who had concurrent chronic obstructive pulmonary disease or other pulmonary problems.

Fourth, to preserve blinding, we accompanied our single dose of dexamethasone with 4 days of placebo; it is not clear from our results whether this strategy was identical to a single dose of dexamethasone alone or whether the addition of placebo exerted an additional independent effect.

Fifth, this study took place at a single-site urban underserved county hospital, which could limit generalizability to other settings.

DISCUSSION

In this trial comparing a single dose of dexamethasone 12 mg plus placebo to 5 days of prednisone 60 mg in acute asthma, we found 14-day relapse to differ by only 2.3% (95% CI –4.1% to 8.6%). The upper 95% confidence limit of this difference, 8.6%, exceeded our prespecified noninferiority limit of 8.0%; thus, this trial cannot confirm the noninferiority of single dose dexamethasone to 5 days of prednisone in the treatment of mild to moderate asthma exacerbations in the ED. It is unclear whether such a small difference from the preset threshold of 8.0% precludes any clinical significance of our findings. Dexamethasone showed lower relapse rates compared with historical relapse rates both nationally and per our electronic database records (12.1% versus 16%), and it performed substantially

Table 1. Baseline characteristics.*

Variable	Prednisone	Dexamethasone
Number analyzed	203	173
Age, median (IQR), y	32 (25–44)	32 (26–42)
Sex, female	95 (46.8)	89 (51.4)
Race/ethnicity		
Black	118 (58.1)	92 (53.2)
Latino	41 (20.2)	43 (24.9)
White	20 (9.8)	18 (10.4)
Other	23 (11.3)	20 (11.6)
Home inhaled steroids	30 (14.8)	29 (16.8)
Exhausted supply of asthma medications	133 (65.5)	124 (71.7)
ED visit in past 4 wk	18 (8.9)	22 (12.7)
Admission in past 12 mo	32 (15.8)	26 (15.0)
Intubation for asthma	25 (12.3)	17 (9.8)
Current smoker	64 (31.5)	41 (23.7)
Duration of symptoms, median (IQR)	3 (1–7)	3 (1–7)
Vital signs at presentation, mean (SD)		
Initial pulse rate, beats/min	88 (17)	91 (13)
Initial respiratory rate, breaths/min	19 (3)	19 (5)
Initial oxygen saturation, %	97 (3)	97 (2)
Initial peak flow, LPM, mean (SD)	253 (96)	252 (111)
Received continuous nebs	30 (14.8)	21 (12.1)
Number of albuterol treatments, median (IQR)	3 (3–3)	3 (3–3)
Number of Ipratropium Bromide treatments, median (IQR)	1 (1–1)	1 (1–1)
Discharge peak flow, mean (SD)	381 (133)	368 (125)
Prescribed inhaled steroids at discharge	54 (26.6)	30 (17.3)

IQR, Interquartile range; *LPM*, liters per minute; *SD*, standard deviation.
*Data presented as No. (%) unless otherwise noted.

better than placebo, retaining greater than 90% superiority to placebo relapse rates reported previously of 33%.[20]

Because of dexamethasone's long half-life of up to 72 hours and good bioavailability, we identified it as a good candidate for a single-dose agent in the treatment of acute asthma.[7-10] In the pediatric literature, Qureshi et al[13] reported on a randomized trial suggesting equivalence of 2 days of oral dexamethasone and 5 days of prednisone, demonstrating no difference in relapse rates and symptoms in children at 10 days of follow-up. Altamimi et al[11] compared a single dose of oral dexamethasone to 5 days of prednisolone in a randomized, double-blind study. The study, however, did not reach statistical significance because of insufficient enrollment but did suggest equivalence with similar rates of return-to-baseline patient self-assessment scores on reevaluation at 5 days. Also in the pediatric literature, Gordon et al[12] investigated a single dose of intramuscular dexamethasone and showed no difference in the change of the asthma score compared with that for 5 days of prednisolone at a 4-day follow-up visit. For our study, we chose the oral form of dexamethasone instead of intramuscular. These 2 routes demonstrate similar bioavailability and relapse rates.[5] Most recently in the adult literature, Kravitz et al[14] determined that a 2-day course of oral dexamethasone is at least as effective as 5 days of oral prednisone, with a return to daily activities at 3 days as determined by a telephone follow-up visit at 2 weeks. Relapse rates were similar between the 2 groups.

One of the largest benefits of a single dose of oral dexamethasone comes from the likelihood of improved compliance. The medication may be administered in the ED or office setting without any requirement for filling a prescription and then receiving the medication as prescribed at home. Krishnan et al[15] evaluated compliance rates after discharge of patients who had been hospitalized

Table 2. Results.

Outcome Measures	Prednisone, %	Dexamethasone, %	Diff, %	95% CI
Any ED visit in last 14 days	9.8	12.1	2.3	−4.1 to 8.6
Any hospital admission in last 14 days	2.9	3.4	0.5	−4.1 to 3.1
Feels better with pills*	64.5	59.5	−5.0	−4.8 to 14.8
No. home albuterol treatments, mean (SD)†	2.86 (0.79)	2.78 (1.02)	−0.08	−0.03 to 2.0
Residual symptoms				
Wheezing	31.0	35.3	4.2	−5.3 to 13.8
Shortness of breath	32.5	29.5	−3.0	−6.3 to 12.4
Cough	37.9	33.5	−4.4	−5.3 to 14.1
Difficulty with ADLs	15.3	16.2	0.9	−6.4 to 8.3
Completed study medications	91.3	93.1	1.7	−3.6 to 7.2
Any adverse reaction	28.6	24.3	−4.3	−4.6 to 13
Sleep disturbance	6.4	3.5	−2.9	−1.4 to 7.3
Abdominal pain	4.9	1.1	−3.8	0.4 to 7.1
Vomiting	2.5	1.1	−1.3	−1.3 to 3.9
Mood disturbance	2.5	2.3	−0.2	−2.9 to 3.2
Other	15.2	15.0	−0.2	−7.5 to 7.0

ADLs, Activities of daily living.
*Compares "yes" to "no" and "don't know."
†Somer's D of the difference.

for asthma, using electronic monitors. Adherence at 7 days for oral and inhaled corticosteroids was 50%. Poor adherence significantly predicted significantly worsened symptom control. A single dose of medication eliminated prescription adherence barriers such as forgetfulness, cost, and dose omission.[16] Thomas et al[23] showed a correlation between a subject's not obtaining medication and a lack of insurance and dissatisfaction with discharge instructions. In a related study, Saunders[24] demonstrated that at least 20% of patients do not even fill their ED prescriptions after discharge. Our study nearly reached statistical significance of noninferiority despite providing the 4 additional doses of prednisone, thus nullifying the prescription-filling obstacle to adherence. If 20% of subjects had not filled the prednisone prescription, the relapse rate possibly would have trended toward the national average of 16%.

In summary, our study by a small margin did not demonstrate noninferiority of a single dose of dexamethasone to 5 days of prednisone for adult patients with mild to moderate acute asthma exacerbations for prevention of relapse. However, enhanced compliance and convenience may support the use of a single oral dose of dexamethasone regardless.

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Author contributions: MWR and HJA conceived the study, designed the trial, obtained research funding, and supervised the conduct of the trial and data collection. MWR and MR undertook recruitment of patients and managed the data, including quality control. MWR, BL, and HJA analyzed the data and drafted the article. All authors contributed substantially to article revision. MWR takes responsibility for the paper as a whole.

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REFERENCES

1. Moorman JE. National surveillance of asthma: United States, 2001-2010. *Vital Health Stat 3*. 2012;(35):1-67.
2. Rowe BH, Spooner CH, Ducharme FM, et al. Corticosteroids for preventing relapse following acute exacerbations of asthma. *Cochrane Database Syst Rev*. 2001:CD000195.
3. Barnett PLG, Caputo GL, Baskin M, et al. Intravenous versus oral corticosteroids in the management of acute asthma in children. *Ann Emerg Med*. 1997;29:212-217.
4. Becker JM, Arora A, Scarfone RJ, et al. Oral versus intravenous corticosteroids in children hospitalized with asthma. *J Allergy Clin Immunol*. 1999;103:586-590.
5. Krishnan JA, Nowak R, Davis SQ, et al. Anti-inflammatory treatment after discharge home from the emergency department in adults with acute asthma. *J Emerg Med*. 2009;37(2 suppl):S35-S41.
6. National Asthma Education and Prevention Program. *Guidelines for the Diagnosis and Management of Asthma. Expert Panel Report 3*. Bethesda, MD: National Institutes of Health; 2007:1-404.
7. Dernedorf H, Hochlaus G, Mollmann H. Receptor based pharmacokinetics—pharmacodynamics analysis of corticosteroids. *J Clin Pharmacol*. 1993;33:115-123.
8. Egerman RS, Pierce WF 4th, Andersen RN, et al. A comparison of the bioavailability of oral and intramuscular dexamethasone in women in late pregnancy. *Obstet Gynecol*. 1997;89:276-280.
9. Elliott CL, Read GF, Wallace EM. The pharmacokinetics of oral and intramuscular administration of dexamethasone in late pregnancy. *Acta Obstet Gynecol Scand*. 1996;75:213-216.
10. Tóth GG, Kloosterman C, Uges DR, et al. Pharmacokinetics of high-dose oral and intravenous dexamethasone. *Ther Drug Monit*. 1999;21:532-535.
11. Altamimi S, Robertson G, Jastaniah W, et al. Single-dose oral dexamethasone in the emergency management of children with exacerbations of mild to moderate asthma. *Pediatr Emerg Care*. 2006;22:786-793.
12. Gordon S, Tompkins T, Dayan PS. Randomized trial of single-dose intramuscular dexamethasone compared with prednisolone for children with acute asthma. *Pediatr Emerg Care*. 2007;23:521.
13. Qureshi F, Zaritsky A, Poirier MP. Comparative efficacy of oral dexamethasone versus oral prednisone in acute pediatric asthma. *J Pediatr*. 2001;139:20.
14. Kravitz J, Dominici P, Ufberg J, et al. Two days of dexamethasone versus 5 days of prednisone in the treatment of acute asthma: a randomized controlled trial. *Ann Emerg Med*. 2011;58:200-204.
15. Krishnan JA, Riekert KA, McCoy JV, et al. Corticosteroid use after hospital discharge among high-risk adults with asthma. *Am J Respir Crit Care Med*. 2004;170:1281-1285.
16. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353:487-497.
17. Lahn M, Bijur P, Gallagher EJ. Randomized clinical trial of intramuscular vs oral methylprednisolone in the treatment of asthma exacerbations following discharge from an emergency department. *Chest*. 2004;126:362.
18. Krishnan JA, Lemenske RF Jr, Canino GJ, et al. Asthma outcomes: symptoms. *J Allergy Clin Immunol*. 2012;129(3 suppl):S124-S135.
19. Emerman CL, Woodruff PG, Cydulka RK, et al. Prospective multicenter study of relapse following treatment for acute asthma among adults presenting to the emergency department. *Chest*. 1999;115:919-927.
20. Chapman KR, Verbeek PR, White JG, et al. Effect of a short course of prednisone in the prevention of early relapse after the emergency room treatment of acute asthma. *N Engl J Med*. 1991;324:788-794.
21. D'Agostino RD, Massaro JM, Sullivan LM. Non-inferiority trials: design concepts and issues—the encounters of academic consultants in statistics. *Stat Med*. 2003;22:169-186.
22. Gould AL, Shih JW. Modifying the design of ongoing trials without unblinding. *Stat Med*. 1998;17:89-100.
23. Thomas EJ, Burstin HR, O'Neil AC, et al. Patient non-compliance with medical advice after the emergency department visit. *Ann Emerg Med*. 1996;27:49-55.
24. Saunders CE. Patient compliance in filling their prescriptions after discharge from the emergency department. *Am J Emerg Med*. 1987;5:283-286.