# A meta-analysis of the effect of oral and inhaled corticosteroids on growth

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*This analysis summarizes studies comparing attained heights with expected heights of children with asthma treated with inhaled or oral corticosteroids. The possible moderating effects of treatment duration, and dosage and asthma severity are also examined. A preliminary database of 95 articles rendered 21 includable studies representing 810 patients with asthma, which yielded 29 tests of the corticosteroid-growth effect. Statistical integration of the results of these studies revealed a significant but small tendency for corticosteroid therapy in general to be associated with diminished final height ($Z = 2.328$, $p = 0.01$, mean $r = -0.023$). However, this effect varied for the specific drugs under consideration. As expected, significant weak growth impairment was observed for prednisone ($Z = 2.137$, $p = 0.0164$, mean $r = -0.295$) and "other oral corticosteroids" ($Z = 9.107$, $p = 2.44E\text{-}18$, mean $r = -0.260$). On the other hand, a significant moderate tendency was observed for inhaled beclomethansone dipropionate therapy to be associated with attaining* normal *stature ($Z = 7.395$, $p = 2.17E\text{-}13$, mean $r = +0.432$). There was no statistical evidence for beclomethasone dipropionate therapy to be associated with growth impairment at higher doses, for longer therapy durations, or among patients with more severe asthma. This meta-analytic integration indicates that available studies of inhaled beclomethasone dipropionate therapy do not show an association between its use and the adverse effect of diminished stature. (J ALLERGY CLIN IMMUNOL 1994;93:967-76.)*

***Key words:*** *Asthma, inhaled corticosteroids, growth, steroid-dependent asthma*

Because of the importance of airway inflammation in the pathogenesis of asthma, inhaled corticosteroids (ICs) are emerging as preferred agents of prophylaxis for asthma.[1] The 1991 National Asthma Education Program "Guidelines for the Diagnosis and Management of Asthma" concluded that "inhaled corticosteroids are safe and effective for the treatment of asthma."[2] In spite of this optimism, serious concern about adverse effects of ICs persists. One of the most frequently cited and controversial potential side effects of repeated use of ICs is growth retardation in children. Although most studies have failed to show an adverse effect of ICs on linear growth, several case reports to the contrary have appeared.[3] Further, a recent prospective comparison of theophylline and inhaled beclomethasone dipropionate (BDP) therapy for asthma concluded that BDP therapy was effective, "but that caution must be used with administration of beclomethasone dipropionate in children because of the growth velocity suppression."[4] The current consensus is summarized by Konig's conclusion that "Although the overwhelming majority of studies demonstrate no effect on growth, some patients, on larger doses, dependent perhaps on individual sensitivity, may exhibit some growth retardation."[5] The degree to which such detectable slowing of growth velocity has clinically significant effects on height remains uncertain.

This study attempts to integrate multiple investigations of the effects of inhaled and oral

*Abbreviations used*
BDP: Beclomethasone dipropionate
ICs: Inhaled corticosteroids
k: Number of hypothesis tests in the database

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corticosteroids, used in the treatment of asthma, on linear growth. The strategy pursued is a meta-analytic integration,[6-12] which is an empirical strategy that has had a high success rate in similar domains. Application of meta-analysis to the multiple studies of the effects of ICs on growth is indicated for the following reasons. (1) Although several comprehensive narrative reviews have been published on this topic, substantial differences between the conclusions derived from reviews of scientific literature and those derived from meta-analytic reviews have been repeatedly demonstrated.[13, 14] Meta-analytic techniques allow the investigator to gauge the significance and magnitude of patterns, whereas literature reviews can only suggest such patterns. (2) Meta-analysis can reveal complex and sophisticated relationships among variables in a research domain that would never have become apparent through a literature review of the research. The importance of complicating factors such as differences between specific glucocorticoid preparations, the effect of patient age and pubertal development, duration and dose of corticosteroid therapy, and illness severity on the corticosteroid-growth effect can be examined. (3) ICs are being more commonly used in the treatment of mild-to-moderate asthma, and there is an expanding body of individual studies examining growth of such children. A more precise understanding of the cumulative evidence already available is needed.

## METHODS

Meta-analysis refers to the statistical integration of several independent studies through application of statistical techniques developed and suited for summarizing, integrating, and testing of practical questions and theoretic issues with combined results of previous research.[15-17] Procedurally, the statistical tests (e.g., chi square tests) of a well-defined hypothesis are transduced to common metrics for significance levels (Z and one-tailed $p$ values) and effect size (Z Fisher and $r$ values; described, for example, as *weak* or *moderate*). Once placed on these common metrics, the results of separate hypothesis tests can be combined, compared, and examined for the fit of predictive models.[8-10]

An exhaustive literature search of leading medical journals encompassing the past 37 years and up to January 1993 was conducted. Studies were included if they reported the precise number of patients with asthma receiving corticosteroids who were at or above their expected height for their chronologic age and the precise number of patients with asthma receiving corticosteroids who were below their expected height for their chronologic age (Table I). These frequencies allowed the direct derivation of a one-sample chi-square statistic,[18] testing the association between use of corticosteroids and growth. These one-sample chi square tests were then transduced into the common metrics for significance levels and effect sizes.

Tests were coded as being in a positive direction if the number of patients at or above their expected height was larger than the number of patients below their expected height. In other words, a positive direction of effect means that the use of corticosteroids was associated with attaining normal stature (neither tall nor short). Tests were coded as being in a negative direction if the number of patients at or above their expected height was smaller than the number of patients below their expected height, signifying an association of corticosteroid therapy with being short (Fig. 1). Fig. 1, *a* presents a hypothetical study of 25 patients in which 15 attained heights that were at or above their expected heights, whereas 20 fell below their expected heights ($\chi^2[1] = 0.714$). Because more patients were shorter than their expected heights, this chi square test result is transformed into a negative effect size of $r = -0.143$. Fig. 1, *b* presents a hypothetical study of 35 patients in which 23 attained heights that were at or above their expected heights, whereas 12 fell below their expected heights ($X_2[1] = 3.457$, $r = +0.314$; formulas and computational procedures for these transformations are presented).[8, 10]

To focus on tests of the corticosteroid-growth effect in studies that were optimally homogeneous in methodologic and statistical terms, qualitatively different determinations of "growth" (e.g., short-term knemometry studies)[19] and studies in which parametric inferential statistics were used (e.g., analysis of average heights)[20] were not included in the present effort. A total of 95 published and unpublished papers and reports were examined, rendering a total of 21 includable studies. These 21 studies yielded a total number of hypothesis tests in the database (k) of 29 separate tests of the corticosteroid-growth effect, representing the data for 810 patients with asthma receiving corticosteroids.

The specific corticosteroid used in each study was classified into one of three categories for analysis: (1) BDP (k = 12 hypothesis tests); (2) prednisone (k = 7 hypothesis tests); or (3) "other" oral corticosteroids (k = 10 hypothesis tests). It was only within the more frequent hypothesis tests with inhaled BDP that sufficient information was available to examine the following predictors: (1) patient age (in years), (2) therapy duration (in years), (3) dosage (μg/day), (4) asthma severity (verbal descriptions of patients were classified as either low severity [e.g., "asthmatics," "asthma"] or high severity [e.g., "steroid-dependent asthmatics," "intractable asthma"]). Each of the included hypothesis tests, along with the corresponding predictors, is presented in Table I.

**TABLE I.** Studies included in the meta-analytic database

| Study | $\chi^2$ (1) | N | DOE* | r | Drug | Dosage (mg/day) | Duration (yr) | Age (yr)† | Severity of asthma |
|---|---|---|---|---|---|---|---|---|---|
| Bager et al. (63) | 27.222 | 45 | − | 0.778 | P | — | — | — | — |
| Bahn et al. (80) | 4.900 | 40 | + | 0.350 | BDP | 471 | 3.8 | 10.2 | [0] |
| Balfour-Lynn (86) | 2.793 | 29 | + | 0.310 | BDP | 469 | 5.8 | 7.5 | [0] |
| Brown et al. (80) | 12.565 | 23 | + | 0.739 | BDP | 336 | 4.9 | 8.0 | [1] |
| Brown et al. (80) | 30.769 | 52 | + | 0.769 | BDP | 336 | 4.9 | 8.0 | [0] |
| Chang et al. (82) | 14.700 | 46 | − | 0.565 | O | — | — | — | — |
| Chang et al. (82) | 34.680 | 75 | − | 0.680 | O | — | — | — | — |
| Chang et al. (82) | 26.947 | 38 | − | 0.842 | O | — | — | — | — |
| Chang et al. (82) | 29.455 | 44 | − | 0.818 | O | — | — | — | — |
| Delacourt et al. (91) | 28.888 | 50 | + | 0.760 | BDP | 875 | 1.6 | 10.8 | [1] |
| Dutau & Rochiccioli (78) | 8.167 | 24 | + | 0.583 | BDP | 400 | 0.9 | 7.8 | [0] |
| Falliers et al. (63) | 3.769 | 13 | + | 0.538 | O | — | — | — | — |
| Falliers et al. (63) | 0.444 | 36 | − | 0.111 | P | — | — | — | — |
| Falliers et al. (63) | 1.333 | 12 | + | 0.333 | O | — | — | — | — |
| Francis (76) | 0.600 | 15 | − | 0.200 | BDP | 300 | 0.2 | 10.7 | [1] |
| Godfrey & König (74) | 0.000 | 26 | + | 0.000 | BDP | 469 | 1.3 | 9.1 | [1] |
| Godfrey et al. (78) | 4.263 | 19 | − | 0.474 | BDP | 400 | 3.7 | 12.5 | [1] |
| Graff-Lonnevig & Kraepelien (79) | 1.581 | 31 | − | 0.226 | BDP | 400 | 2.1 | 9.4 | [1] |
| Kerribijn (76) | 0.143 | 7 | + | 0.143 | BDP | 300 | 1.5 | 10.4 | [0] |
| Kuzemko (74) | 4.500 | 8 | + | 0.750 | O | — | — | — | — |
| Kuzemko (74) | 0.500 | 8 | − | 0.250 | P | — | — | — | — |
| Morris (75) | 3.600 | 10 | − | 0.600 | P | — | — | — | — |
| Morris (75) | 3.600 | 10 | − | 0.600 | P | — | — | — | — |
| Reimer et al. (75) | 8.000 | 18 | − | 0.667 | P | — | — | — | — |
| Smith (65) | 25.000 | 49 | + | 0.714 | P | — | — | — | — |
| Tarada (81) | 3.267 | 15 | + | 0.467 | BDP | 200 | 1.5 | 9.1 | [0] |
| VanMetre et al. (60) | 12.800 | 20 | − | 0.800 | P | — | — | — | — |
| VanMetre et al. (60) | 0.529 | 17 | − | 0.176 | O | — | — | — | — |
| VanMetre et al. (60) | 14.000 | 14 | + | 0.999 | O | — | — | — | — |
| Varsano et al. (90) | 0.250 | 16 | + | 0.125 | O | — | — | — | — |
| Westphal (68) | 9.000 | 16 | − | 0.750 | O | — | — | — | — |

In the first column numbers in parentheses are degrees of freedom.

*N*, Number of patients; *DOE*, direction of effect; *r*, product moment correlation (magnitude of effect); *P*, prednisone; *O*, "other corticosteroids;" *[0]*, low severity; *[1]*, high severity.

*Where plus sign (+) indicates that number of patients at or above their expected height was greater than number of patients below their expected height, and minus sign (−) indicates that number of patients at or above their expected height was smaller than number of patients below their expected height.

† Patient sample age.

## RESULTS

### General effect

There was a significant but small tendency for corticosteroid therapy in general to be associated with being shorter than one's expected height ($Z = 2.328$, $p = 0.0100$, mean $r = -0.023$). A fail-safe number of Nfs ($p = 0.05$) = 2.1 was obtained, indicating that only two additional studies that average no association between corticosteroid use and growth would be needed to reduce the combined $p$ value of 0.0100 to the "just barely" significant $p$ value of 0.05. This low fail-safe number indicates a weak effect, which could be disconfirmed by relatively few contradictory studies (i.e., not robust to future disconfirmations).

1.a. Hypothetical study showing a weak tendency for the use of corticosteroids to be associated with being short.

| # of patients below expected height | # of patients at or above expected height |
|---|---|
| 20 | 15 |

$\chi^2_{(1)} = 0.714$
$r = -.143$

1.b. Hypothetical study showing a moderate tendency for the use of corticosteroids to be associated with being short.

| # of patients below expected height | # of patients at or above expected height |
|---|---|
| 12 | 23 |

$\chi^2_{(1)} = 3.457$
$r = +.314$

**FIG. 1.** Hypothetical studies illustrating the type of data used to extract tests of the effect of corticosteroids on growth.

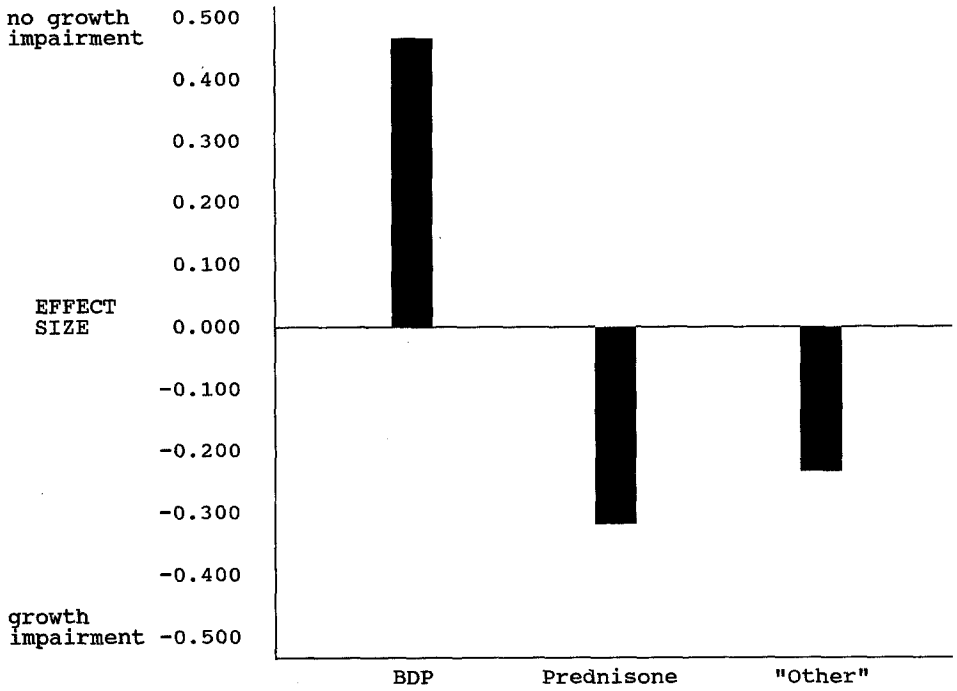


**FIG. 2.** Effects of specific corticosteroids on the growth of children with asthma.

## Effects of specific drugs

The effect of corticosteroids on growth varied with the specific drug used (Fig. 2). Oral prednisone therapy (k = 7 hypothesis tests) showed a significant moderate tendency to be associated with being shorter than expected (Z = 2.137, $p = 0.0164$, mean $r = -0.295$). A fail-safe number of Nfs($p = 0.05$) = 38.4 was obtained, indicating that approximately 38 additional studies averaging no association between corticosteroid use and growth would be needed to reduce the combined $p$ value of 0.0164 to the "just barely" significant $p$ value of 0.05. This fail-safe number of 38 approaches the benchmark of 5k + 10 studies[21] (which in this case would be 5[7] + 10 = 45 studies), indicating an effect that is relatively robust to future disconfirmations. For "other" oral corticosteroids (k = 10), there was also a

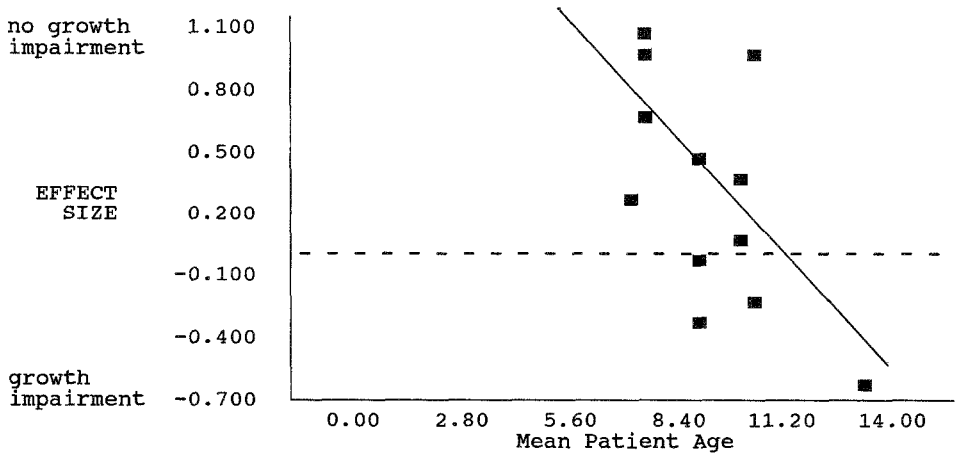


**FIG. 3.** Prediction of magnitude of effect of inhaled BDP on growth by patient age (in years).

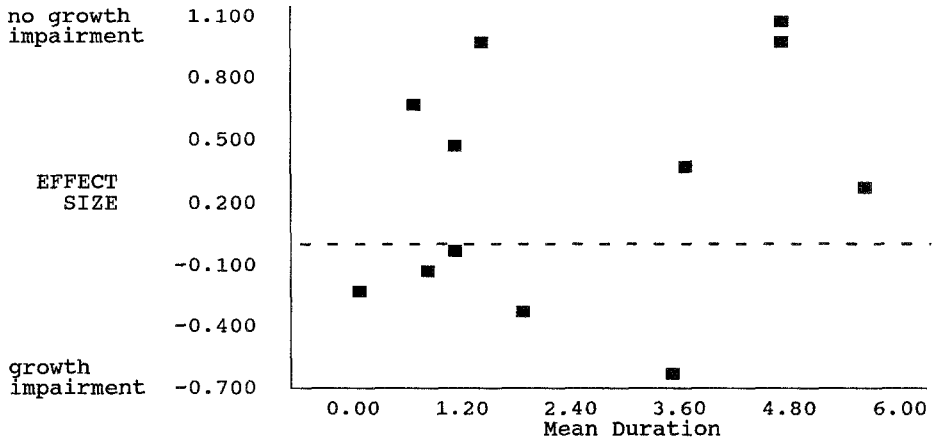


**FIG. 4.** Prediction of magnitude of effect of inhaled BDP on growth by treatment duration (in years).

significant weak tendency to be associated with being shorter than expected height (Z = 9.107, $p$ = 2.44E-18, mean $r$ = −0.260). A fail-safe number of Nfs($p$ = 0.05) = 93.5 was obtained, indicating that this effect is relatively robust to future disconfirmations.

BDP therapy (k = 12), on the contrary, showed a significant moderate tendency to be associated with normal stature (Z = 7.395, $p$ = 2.17E-13, mean $r$ = +0.432). A fail-safe number of Nfs ($p$ = 0.05) = 125.6 was obtained, indicating that this effect (i.e., lack of detrimental effect on final height) is robust to future disconfirmations. Each of the following predictors was examined for those studies of growth of children with asthma treated with inhaled BDP.

### Effects of patient age

The growth-retarding effect of BDP therapy appeared to vary as a function of patient age (Fig. 3). The correlation between the magnitude of BPD's effect on growth and patient age was $r$ = −0.568 (Z = 4.058, $p$ = 0.0000249). The regression line that captures the prediction of the BDP-growth effect as a function of patient sample age (i.e., Z Fisher = 2.159 − .0.193[age]) indicates that at the age of 11.2 years, the predicted BPD-growth effect equals zero. This may suggest an age beyond which the use of inhaled BDP is more likely to cause growth impairment, perhaps related to inhibition of the normal increase in growth hormone secretion during puberty. However, a more plausible explanation is that the delayed sexual development observed in many children with asthma results in slowed growth when compared with pubertal peers.

### Effects of therapy duration

Surprisingly, greater duration of BDP therapy showed a significant prediction toward no impair-

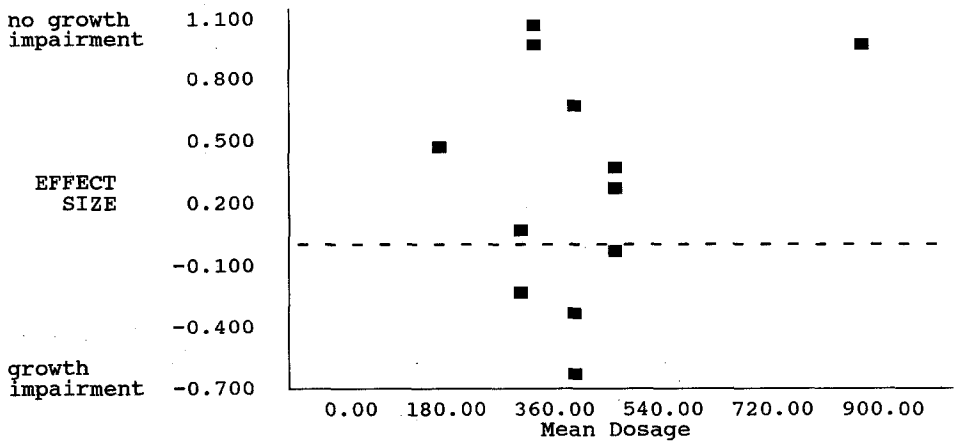


**FIG. 5.** Prediction of magnitude of effect of inhaled BDP on growth by dosage (in micrograms per day).

ment in growth ($p = +0.273$, $Z = 1.977$, $p = 0.0240$) (Fig. 4). In other words, more prolonged BDP therapy was not associated with greater growth impairment. There is the possibility of a confounding influence between age and treatment duration (e.g., longer durations might only be possible for older patients). Therefore effects of each predictor were examined after partialling out effects of the other. These analyses suggest that increasing age ($r = -0.505$, $Z = 3.635$, $p = 0.00139$) remains a potent independent predictor of growth impairment during BDP therapy. However, the predictive power of treatment duration ($r = +0.086$, $Z = 0.624$, $p = 0.2662$) is eliminated when the effects of age are partialled out.

### Effects of dosage

There was a significant prediction of an absence of growth impairment as a function of BDP dosage levels ($r = +0.263$, $Z = 2.144$, $p = 0.0160$) (Fig. 5). This observation, which is contrary to previous descriptions of the effects of IC dosage on growth,[22-24] suggests that currently available evidence fails to show that greater doses of BDP are more likely to result in growth failure. However, few studies examining higher dose BDP therapy in children have been performed.

### Effects of illness severity

Greater dosages of BDP would be expected to be used in samples of patients with more severe asthma. There was a nonsignificant trend in this direction, with the mean dosage for studies of samples with less severe asthma (362.7 μg/day) being less than the mean dosage for studies of samples with more severe asthma (463.3 μg/day, $p = 0.159$). In spite of the nonsignificance of this trend, interactive effects of dosage and severity were examined, to ensure the absence of any confounding influence of one predictor on the other.

Patients with "severe" asthma demonstrated a significantly ($Z = 2.318, p = 0.0102$) weaker positive effect for attaining normal stature ($k = 6$, $Z = 3.593, p = 0.000163$, mean $r = +0.305$) than patients with less severe asthma ($k = 6$, $Z = 6.765$, $p = 1.21E\text{-}11$, mean $r = +0.543$). However, these data do not indicate that growth was impaired by BDP therapy among patients with more severe asthma; even among these patients, the association between BDP treatment and the attainment of normal stature was significant and of moderate magnitude.

In light of the anticipated relationship between BDP dosage and illness severity, the interactive effects of dosage and severity were examined. A significant ($Z = 3.704$, $p = 0.000106$) interaction between dosage levels and sample asthma severity was observed. The effects on growth of each combination of high and low severity (as defined above) and high (>400 μg/day) and low (<400 μg/day) BDP dosage are shown in Fig. 6. Significant positive effects (i.e., toward no growth impairment) were obtained in all: low severity, low dosage ($Z = 5.831$, $p = 3.32E\text{-}9$, mean $R = +0.681$); low severity, high dosage ($Z = 3.743$, $p = 0.000091$, mean $r = +0.405$); high severity, low dosage ($Z = 2.546$, $p = 0.00545$, mean $r = +0.457$); and high severity, high dosage ($Z = 2.840$, $p = 0.00225$, mean $r = +0.255$). Thus a significant tendency toward growth impairment was not observed with any combination of severity and dosage, although information regard-

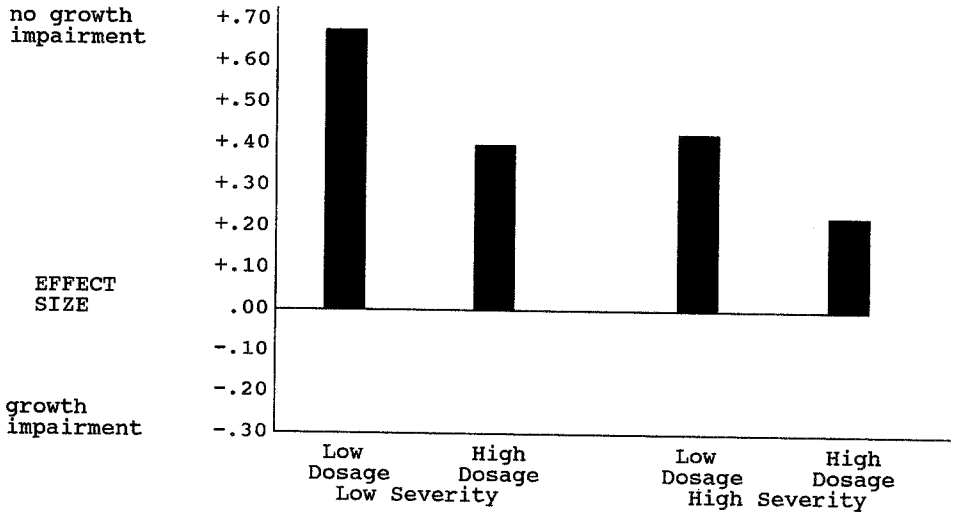


**FIG. 6.** Effects of asthma severity and dosage of inhaled BDP on linear growth.

ing higher BDP dosage (e.g., ≥800 μg/day) is limited.

## DISCUSSION

This meta-analytic integration reinforces a significant but weak tendency for corticosteroid (in general) used in the treatment of asthma to be associated with growth impairment. This tendency, however, is dependent on the specific corticosteroid used; that is, prednisone and "other oral corticosteroids" appear to be associated with significant small degrees of growth impairment, whereas inhaled BDP, on the other hand, shows a significant tendency to be associated with attaining normal stature. Inhaled BDP therapy for childhood asthma appears to be relatively independent of the purported side effect of growth impairment.

A few intriguing patterns emerged from studies examining the effect of BDP on growth. First, growth impairment appeared slightly more likely after 11 years of age. Such an effect might indicate greater sensitivity of the growth hormone axis to suppression by glucocorticoids during the normal acceleration of growth in puberty.[25] An alternative and perhaps more likely explanation is that delayed growth and maturation commonly observed in children with asthma (independent of drug therapy) results in relative slowing of growth rate compared with the normally accelerated growth of pubertal peers. The data also suggest that younger patients are comparatively safe from BDP-induced growth impairment. Second, analysis of duration of BDP therapy did not reveal accumulation of growth retardation with prolonged treatment. This suggests that short-term decrements in growth velocity observed by some investigators may not be sustained over time. Third, the weight of available evidence failed to reveal greater growth impairment at higher doses; that is, the currently available evidence does not substantiate the assumed positive relationship between BDP dose and growth retardation. Even under conditions of "high" illness severity and "high" (>400 μg/day) BDP dosage, in which one might expect an adverse effect of BDP on growth to emerge, there was a remarkably robust failure for BDP to be associated with growth impairment. It is acknowledged, however, that the effect on growth of doses of BDP significantly higher than that currently recommended (e.g., >800 μg/day) remains uncertain.

A valid criticism of this study is that the attainment of a normal height for age does not directly address whether ICs can adversely affect growth velocity independent of the effect of asthma itself. A recent study[4] concludes that inhaled BDP therapy is effective, "but that caution must be used with administration of beclomethasone dipropionate in children because of the growth velocity suppression." It is true that observed short-term reductions in growth velocity suggest the possibility for long-term consequences for relative stature during childhood or adulthood. Prolonged moderate impairment in growth velocity during childhood may eventually result in adult short stature. However, the long-term clinical relevance of this conclusion would appear to be in question on the basis of available evidence integrated above: the cumulative results of 12

studies of actual height attained by children treated with BDP reveal a significant moderate tendency for BDP therapy to be associated with attaining normal stature ($Z = 7.395$, $p = 2.17E\text{-}13$, mean $r = +0.432$). Thus although the use of inhaled BDP might impair the rate of growth of some children, it does not predictably impair the eventual attainment of expected height.

However, this reconciliation between normal height for age in spite of transient impairment in growth rate begs the question of whether inhaled BDP actually has short-term growth-retarding effects. This issue remains controversial, and most investigators have concluded that treatment with inhaled BDP does not adversely affect growth velocity. The data from a recent study[4] reporting slowing of growth velocity in BDP-treated versus theophylline-treated children with asthma are actually underwhelming in this regard: based on the growth velocity data for the 86 patients treated with BDP studied, a chi square value of $X_2(1) = 1.163$, $p = 0.1404$, $r = -0.116$ is obtained, indicating a weak nonsignificant impairment in observed versus expected growth velocity. (Note: an untreated control population was not studied, and theophylline-treated individuals grew somewhat faster than expected during the study period.) The integration of this study with additional studies[26-28] reporting results for growth velocity reveals a nonsignificant and negligible tendency for inhaled BDP to be associated with a reduced growth velocity ($Z = 0.922$, $p = 0.1784$, mean $r = -0.052$).

In a convincing long-term study, Balfour-Lynn[29] reported that children with asthma receiving long-term treatment with BDP (400 to 600 μg/day), after a period of delayed pubertal growth acceleration, eventually attained normal predicted final adult height (based on parental heights). The appearance of growth retardation in children treated with BDP was attributed to delayed growth, which was ultimately achieved. Godfrey et al. observed unaltered growth velocity and height centile position during 13 to 20 months[30] and 3 to 5 years[31] of BDP treatment. The findings of additional studies with duration of follow-up greater than 12 months justify the conclusion that long-term BDP treatment in doses of 400 μg/day or less has little or no effect on the mean growth rate of study populations of children with asthma.

Virtually all of the studies cited above have implemented statistical analysis of population mean growth velocities to ascertain the effect of ICs. The results of such studies convincingly alleviate concern about growth retardation as an expected adverse effect, which could potentially limit acceptance and usefulness of such medications. However, detection of unexpected or idiosyncratic adverse responses to ICs requires close examination of data on individuals in these studies. For example, Godfrey and Konig[30] report observed mean growth velocity (4.9 cm/yr) equal to mean expected growth velocity (5.0 cm/yr) in 26 children treated with BDP. However, examination of individual data reveals that 5 of 26 children grew at a rate ≥1.5 cm/yr slower than expected, suggesting that these particular subjects may have experienced BDP-induced growth retardation. Anecdotal but well-documented reports of severe growth failure caused by IC therapy[3] indicate that some children are at risk of experiencing adverse effects when receiving doses of ICs normally considered to be safe. Although not yet proven, intensified systemic effects from ICs probably reflect variations in receptor affinity, absorption, metabolism, or excretion of glucocorticoids, which cannot presently be predicted.

Collectively, the studies integrated by this meta-analysis justify the following conclusions regarding inhaled BDP therapy and growth. (1) In the treatment of chronic severe asthma, substitution of oral corticosteroid therapy with BDP therapy significantly reduces the risk of growth retardation. (2) In the treatment of the much larger population of children with mild-to-moderate asthma, moderate-dose BDP therapy is unlikely to have a clinically significant effect on linear growth and should be considered safe treatment in this regard. (3) Higher doses of ICs (≥800 μg/day) might be expected to result in more frequent and profound growth suppression; although further studies are needed, the available information does not confirm this expectation. On the basis of current cumulative information, inhaled BDP therapy is associated with the attainment of normal stature. Detectable reductions in growth velocity may occasionally occur. Although the relevance of this to the attainment of normal height is not substantiated by this study, it is appropriate to advise children who are treated with BDP and their families of the risk for idiosyncratic responses manifest as significant growth impairment, to inform them about the low probability of this risk, and to carefully monitor the linear growth of children with asthma treated with ICs.

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