

# PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

## **Use of Aromatase Inhibitors in Children and Adolescents With Disorders of Growth and Adolescent Development**

Dorothy I. Shulman, Gary L. Francis, Mark R. Palmert, Erica A. Eugster and for the Lawson Wilkins Pediatric Endocrine Society Drug and Therapeutics Committee

*Pediatrics* 2008;121:e975-e983

DOI: 10.1542/peds.2007-2081

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://www.pediatrics.org/cgi/content/full/121/4/e975>

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2008 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



# Use of Aromatase Inhibitors in Children and Adolescents With Disorders of Growth and Adolescent Development

Dorothy I. Shulman, MD<sup>a</sup>, Gary L. Francis, MD, PhD<sup>b</sup>, Mark R. Palmert, MD, PhD<sup>c</sup>, Erica A. Eugster, MD<sup>d</sup>, for the Lawson Wilkins Pediatric Endocrine Society Drug and Therapeutics Committee

<sup>a</sup>All Children's Hospital, St Petersburg, and Department of Pediatrics, University of South Florida College of Medicine, Tampa, Florida; <sup>b</sup>Department of Pediatrics, Virginia Commonwealth University, Richmond, Virginia; <sup>c</sup>Rainbow Babies and Children's Hospital and Department of Pediatrics, Case Western Reserve University, Cleveland, Ohio; <sup>d</sup>Riley Hospital for Children, Department of Pediatrics, Indiana University School of Medicine, Indianapolis, Indiana

Financial Disclosure: Dr Eugster is a consultant for and has participated in clinical trials sponsored by AstraZeneca. The other authors have indicated they have no financial relationships relevant to this article to disclose.

## ABSTRACT

Although treatment of children and adolescents who have disorders of growth and adolescent development with aromatase inhibitors is increasingly common, data for or against their use are extremely limited. Precocious puberty, short stature, and gynecomastia are conditions for which inhibition of the enzyme aromatase might prove beneficial to reduce clinical signs of estrogenization and/or estrogen-mediated skeletal maturation. In this report, we summarize the published data regarding the use of aromatase inhibitors in these conditions, and review known and potential benefits, safety concerns, and shortcomings of the available information.

USE OF AROMATASE inhibitors (AIs) has now been reported for a wide variety of disorders that range from estrogen-responsive breast cancer and endometriosis in adult women, to peripheral precocious puberty, congenital adrenal hyperplasia (CAH), short stature, and gynecomastia in children and adolescents.<sup>1-5</sup> The use in children and adolescents expanded after the important role of estrogen in skeletal maturation became evident in the mid-1990s after reports of 2 young adult men in their 20s, 1 with an estrogen receptor defect and the other with an inactivating mutation of the aromatase gene. Both were described as having tall stature and unfused epiphyses despite adult pubertal development.<sup>6,7</sup> Other clinical and biochemical features included osteopenia, insulin resistance, elevated serum gonadotropin levels, oligospermia, and impaired sperm motility. In this article, we briefly review the mechanism of action of AIs, describe the currently available agents, and evaluate the published data regarding use of AIs in children and adolescents.

## BACKGROUND

The value of inhibiting aromatase activity developed from the inadvertent discovery that the adrenotoxic, antiepileptic drug aminoglutethimide improved the clinical outcome for patients with breast cancer.<sup>8</sup> Initially, this was attributed to aminoglutethimide-induced blockade of adrenal steroidogenesis. It was not until pioneering work by Thompson and Siiteri<sup>9</sup> that aminoglutethimide was shown to block aromatase (cytochrome P450 XIX [CYP19]) activity. Since that time, numerous compounds have been shown to inhibit this important enzyme.<sup>10</sup>

The aromatase enzyme is a complex formed by 2 proteins, the CYP19 and the nicotinamide-adenine dinucleotide phosphate-cytochrome P450 reductase.<sup>11</sup> There is 1 copy of the CYP19 gene located on chromosome 15q21.2. Tissue-specific expression results from the interplay of 9 promoters that are differentially expressed in various tissues.<sup>10</sup>

The net effect of the aromatase chemical reaction is to aromatize the steroid A ring of androgen substrates resulting in estrogen formation (Fig 1). This is believed to proceed through a sequence of 3 oxygenations at the C-19 position that generate 19-hydroxy and 19,19-dihydroxy intermediates.<sup>12</sup> Subsequently, C-19 and the 1 $\beta$ ,2 $\beta$ -hydrogens are eliminated, resulting in aromatization of the A ring. Although androgens (androstenedione and testosterone) are widely recognized as substrates for aromatase, estrogens are also substrates for aromatase, and their reactions generate catechol estrogen, 2-hydroxyestrogen, and 6 $\alpha$ -hydroxyestrogen that may have critical roles in the induction or promotion of estrogen-responsive malignancies.<sup>12,13</sup> Because of this, both androgens and estrogens act as competitive inhibitors of aromatase, and derivatives of both androgens and estrogens have been tested as AIs.

www.pediatrics.org/cgi/doi/10.1542/peds.2007-2081

doi:10.1542/peds.2007-2081

The recommendations in this article do not indicate an exclusive course of treatment or serve as a standard for medical care. Variations, taking into account individual circumstances, may be appropriate.

Dr Palmert's current affiliation is Department of Pediatrics, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada.

### Key Words

aromatase inhibitors, precocious puberty, gynecomastia, short stature

### Abbreviations

AI—aromatase inhibitor  
CAH—congenital adrenal hyperplasia  
CYP19—cytochrome P450 XIX  
FMPP—familial male precocious puberty  
MAS—McCune-Albright syndrome  
GnRH—gonadotropin-releasing hormone  
BMD—bone mineral density

Accepted for publication Sep 18, 2007

Address correspondence to Dorothy I. Shulman, MD, Endocrinology, Diabetes and Metabolism, All Children's Hospital, 777 4th St South, St Petersburg, FL 33701. E-mail: dshulman@health.usf.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2008 by the American Academy of Pediatrics

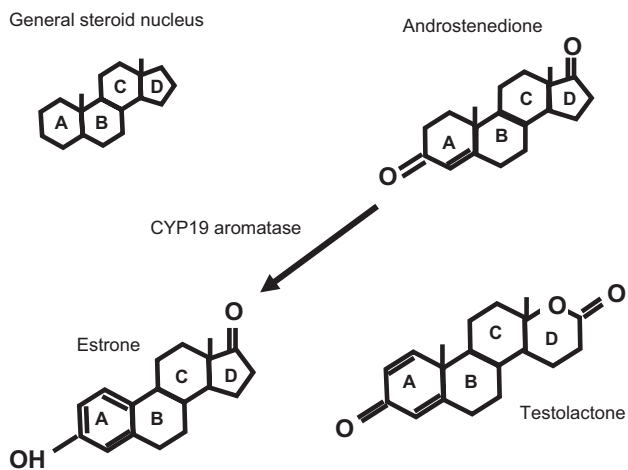


FIGURE 1

Structural comparisons of aromatase substrates. The general steroid ring structure and nomenclature are shown along with the structure of androstenedione, a known substrate for CYP19 (aromatase). Reaction of androstenedione with CYP19 (aromatase) generates the aromatic ring structure in the steroid A ring leading to estrone. For comparison, the structure of testolactone, a widely known inhibitor of CYP19 (aromatase), is shown. Note the similarity in structure to that of androstenedione.

In general, there are 2 distinct structural classes of AIs. Type I, or the steroidal derivatives (Fig 1), are usually derived from androstenedione and irreversibly bind to the catalytic site, a hydrophobic region of the N-terminal sequence, or regions in close proximity.<sup>10,14</sup> Type II, or the nonsteroidal inhibitors (Fig 2), are imidazole/triazole compounds or derivatives of phenobarbitone (eg, aminoglutethimide).<sup>10</sup> Nonsteroidal AIs are characterized by reversible binding to the P450 portion of the aromatase enzyme.

First-generation and second-generation AIs were found to reduce aromatase activity by < 90% (Table 1). The newest, third-generation inhibitors reduce aromatase activity by > 97%.<sup>10</sup> These third-generation nonsteroidal inhibitors are triazole derivatives such as letrozole and anastrozole. They bind to the active site of P450 aromatase through interaction of a heterocyclic nitrogen that is critical for their markedly increased activity.<sup>15</sup> Table 1 lists various AIs, including reputed effectiveness in aromatase inhibition and dosing. In addition to increased potency, third-generation AIs have a longer half-life (2 days) than earlier compounds, allowing once-daily oral administration. The approximate cost of letrozole (2.5 mg) and anastrozole (1 mg) is \$10 a tablet.<sup>16</sup>

### PERIPHERAL PRECOCIOUS PUBERTY

Thus far, AIs have been used as primary treatment in 2 forms of peripheral precocious puberty: familial male precocious puberty (FMPP) and McCune-Albright syndrome (MAS).<sup>17</sup> Although initial experience was gained with first-generation agents, recent interest has focused on the potential use of third-generation AIs, which have greater selectivity, longer half-lives, and increased potency.<sup>18</sup> Progress in this area is hampered by the rarity of these 2 disorders, rendering it difficult to conduct mean-

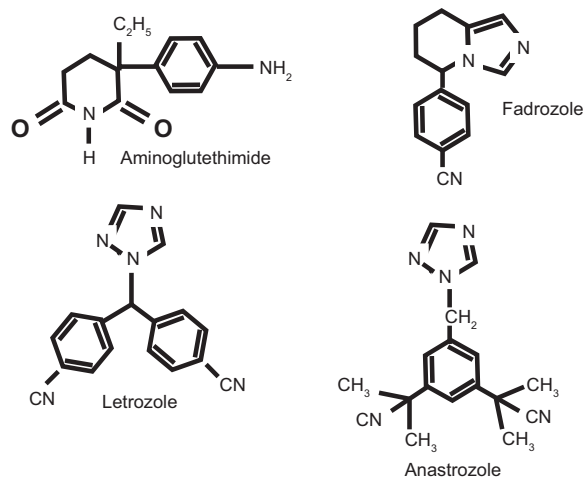


FIGURE 2

Type II, nonsteroidal AIs. The imidazole/triazole compounds or derivatives of phenobarbitone have activity against CYP19 (aromatase), including aminoglutethimide, fadrozole, and more potent third-generation AIs such as letrozole and anastrozole.

ingful clinical trials at a single institution. Rather, multicenter studies are usually necessary to amass a sample size that is sufficient to address questions of safety and efficacy. Fortunately, collaborative research efforts in this area have increased during recent years, which should improve our ability to provide optimal clinical care to affected patients. Contemporary information about the use of AIs in these disorders is reviewed below.

### Familial Male Precocious Puberty

Initial reports of efficacy in the treatment of FMPP with an AI involved the first-generation drug testolactone. When combined with the antiandrogen spironolactone, response to therapy in a small group of boys with FMPP ( $n = 9$ ) was greater compared with that achieved with either compound alone. After  $\geq 6$  months of the combined regimen, growth velocities and rates of skeletal maturation significantly decreased.<sup>19</sup> In addition to beneficial effects on physical parameters, an improvement in aggressive behavior and acne were noted. In a longer term study, testolactone and spironolactone were administered to 8 patients for 2 to 4.2 years, with the addition of the gonadotropin-releasing hormone (GnRH) analog deslorelin with the onset of central puberty. Although this approach was successful in restoring prepubertal growth rates, gonadotropin concentrations, and rates of bone age advancement, no change in

TABLE 1 Relative Potency of Select AIs

Compound	Dosage	% Aromatase Inhibition
Aminoglutethimide	250 mg 4 times daily	90.6
Testolactone	10 mg/kg 4 times daily	<90.0
Formestane	125 mg twice daily	91.9
Fadrozole	2 mg twice daily	92.6
Anastrozole	1 mg once daily	97.3
Letrozole	2.5 mg once daily	>99.1

predicted adult height was noted at the conclusion of the study.<sup>20</sup> In a subsequent follow-up report, however, an average increase in predicted adult height of 12.9 cm was noted after 6 years of combination therapy.<sup>21</sup> Although this was a limited data set, the paucity of other robust treatment options and the positive results effectively established spironolactone and testolactone as first-line treatment for this disorder for many years. With the advent of newer and more potent pharmacologic agents with similar mechanisms of action, attention has now turned to potential alternatives for the treatment of FMPP.<sup>22</sup> Novel combination therapy in the form of the antiandrogen bicalutamide, combined with the third-generation AI anastrozole has now been reported in 2 patients with FMPP, who have been treated for 16 to 44 months. In both boys, striking reductions in growth velocity, rate of skeletal maturation, and pubertal progression have been observed without adverse events.<sup>23</sup> Both medications require once-daily dosing, which represents an additional superior feature over earlier regimens. An international, prospective, multicenter study is under way which will undoubtedly provide valuable information regarding the safety and efficacy of bicalutamide and anastrozole for the treatment of precocious puberty in boys with FMPP.

#### McCune-Albright Syndrome

In contrast to the generally positive results of AIs (combined with antiandrogens) for the treatment of FMPP, experience with this class of compounds in children with MAS has been mixed. To date, limited data are available on the use of first-, second-, and third-generation AIs for the treatment of precocious puberty in this setting, primarily in girls. An initial pilot study of short-term testolactone administration involving 5 girls with MAS seemed beneficial.<sup>24</sup> When patients were followed for a longer period of time, however, a distinct loss of efficacy was noted in many after 3 years of treatment.<sup>25</sup> Not only was there a recurrence of ovarian cysts, but also most patients continued to have periodic vaginal bleeding. Additional difficulties were noted with compliance, because of the 4-times-a-day dosing schedule required when using testolactone. A trial that investigated the second-generation AI fadrazole for the treatment of MAS-associated precocious puberty also proved disappointing.<sup>26</sup> In addition to suboptimal efficacy, fadrazole resulted in a dosage-dependent subclinical inhibition of cortisol and aldosterone biosynthesis, causing additional research efforts with this drug in MAS to be abandoned.<sup>26</sup> In this study, as with testolactone,<sup>25</sup> testosterone and androstenedione levels were mildly elevated above the prepubertal range, but no virilization was observed. Until recently, only anecdotal reports regarding the utility of the third-generation agents anastrozole and letrozole for the treatment of MAS were available<sup>27,28</sup>; however, data from a recently completed multicenter study in which 27 girls with MAS were treated with anastrozole for 1 year have now been analyzed.<sup>29</sup> Anastrozole was ineffective in halting vaginal bleeding and other indices of precocious puberty in these patients; no adverse events were noted. A recently published pilot

study of letrozole in 9 girls who had MAS and precocious puberty and were treated for up to 36 months reported a slowing of growth rate and bone age advancement and fewer episodes of vaginal bleeding<sup>30</sup>; however, by 24 to 36 months, increased ovarian volume and cyst enlargement were observed. One girl experienced ovarian torsion. Given the latter observations, it is reasonable to conclude that no "gold standard" currently exists for the treatment of precocious puberty in children with MAS.<sup>31</sup>

#### CONGENITAL ADRENAL HYPERPLASIA

Judicious treatment of children with CAH can allow them to reach midparental height with traditional therapy (hydrocortisone and fludrocortisone).<sup>32</sup> Poorer height outcomes tend to occur in simple virilizers who begin treatment late or in children who are exposed to equivalent dosages of glucocorticoids >15 mg/m<sup>2</sup> per day of hydrocortisone,<sup>33</sup> or to prednisone.<sup>32</sup> Nonetheless, the average adult height of children who are treated with conventional therapy and appropriate oversight and compliance is approximately -1.4 SD.<sup>34</sup> In some patients, suprphysiologic dosages of glucocorticoids are required to suppress excess adrenal androgen secretion. Either chronic increased androgen secretion or increased glucocorticoid exposure may adversely affect adult height. A long-term clinical trial evaluating the addition of the antiandrogen flutamide (10 mg/kg per day divided twice daily) and the AI testolactone (40 mg/kg per day divided 3 times daily), in addition to a relatively low replacement dosage of hydrocortisone (8 mg/m<sup>2</sup> per day) and fludrocortisone has been under way at the National Institutes of Health since the late 1990s. An interim report described 20 children who were randomly assigned to long-term parallel groups comparing the experimental 4-drug regimen with traditional therapy (hydrocortisone 13 mg/m<sup>2</sup> per day and fludrocortisone).<sup>35</sup> After 2 years, the group that is receiving the experimental treatment regimen had elevated blood androgen levels yet had normal linear growth rate and bone maturation. No significant long-term adverse effects were seen. This trial is still ongoing and has been fully enrolled (32 patients) for 2 years. Patients in the experimental group were switched from testolactone to letrozole after May 2004. Letrozole has been very well tolerated (D. Merke, MD, personal written communication, November 2006). Until these data are critically assessed and published, this therapeutic regimen must be considered experimental.

#### PUBERTAL GYNecomastia

Gynecomastia represents a benign proliferation of the breast glandular tissue and can be detected in up to 60% of boys during puberty. This clinical condition is thought to result from an imbalance of the estrogen stimulatory effects relative to the androgen inhibitory effects at the breast tissue level.<sup>36,37</sup> Histologically, gynecomastia is characterized early by ductal proliferation and the formation of vascular connective tissue. If present beyond 1 year, then chronic fibrous changes may occur associated with dilated ducts and increased stromal hyaliniza-

tion.<sup>38-40</sup> Whereas most pubertal gynecomastia resolves spontaneously, 25% may persist for  $\geq 2$  years.<sup>41</sup> Antiestrogens, nonaromatizable androgens (including dihydrotestosterone), and first-generation AIs have been used to treat gynecomastia with variable success. Most reports include small numbers of patients with no control group.<sup>42-47</sup> In 2004, Plourde et al<sup>5</sup> reported the only randomized, placebo-controlled study performed in adolescents with pubertal gynecomastia using an AI. At the start of the study, patients had gynecomastia that was present for at least 6 months and was stable or increasing. The trial assessed breast volume ultrasonographically in boys aged 11 to 18 years before and after a 6-month trial of anastrozole 1 mg or placebo. A positive response was considered  $> 50\%$  reduction in breast volume. At 6 months, anastrozole significantly increased the testosterone/estradiol ratio compared with pretreatment (166% anastrozole vs 39% placebo), but the percentage of boys with significant reduction in breast volume did not differ between groups (38% vs 31%). Breast pain decreased in both groups. In the anastrozole-treated group, estradiol levels declined 20% and gonadotropin and testosterone levels increased. Biochemical changes did not correlate with clinical response. The authors postulated that if therapy had begun earlier while breast tissue was in a more proliferative stage, then an effect of the AI may have been observed. Also, the estradiol assay used in the study was not very sensitive, and it was difficult to assess the degree of estrogen reduction. The authors suggested that in the presence of even a small amount of estrogen, gynecomastia can persist. Although a more effective enzyme blockade and earlier initiation of therapy may prove beneficial, additional randomized, controlled trials are needed to test these hypotheses before AIs can be endorsed for the treatment of adolescents with pubertal gynecomastia. Lack of sensitivity of commercial estradiol assays<sup>48</sup> may prove to be an obstacle for effective laboratory monitoring of aromatase blockade in adolescents.

In a randomized, placebo-controlled study of 114 adult men who had prostate cancer and were treated with the antiandrogen bicalutamide, the effects of tamoxifen (20 mg/day), an antiestrogen, and anastrozole (1 mg/day) on prevention of gynecomastia were assessed. Tamoxifen significantly reduced the occurrence of gynecomastia after 48 weeks of bicalutamide treatment (10% vs 73% in placebo). The effect of anastrozole did not differ from placebo (51%).<sup>49</sup> It may be that estrogen receptor blockers are a more effective treatment than AIs in the prevention of gynecomastia.

Gynecomastia may occur in boys with aromatase excess associated with Sertoli cell tumors in Peutz-Jeghers syndrome and in families with constitutively active mutations affecting the aromatase gene. Although reports are extremely limited, it has been suggested that gynecomastia in these conditions may be more responsive to AI therapy than is pubertal gynecomastia.<sup>50-53</sup>

## SHORT STATURE

Children with short stature comprise a large portion of the typical pediatric endocrinologist's practice. Current

strategies for increasing adult height include growth hormone treatment alone or together with GnRH analog therapy to suppress pubertal development.<sup>54-56</sup> These approaches are expensive and invasive (requiring injections), and GnRH analog therapy may result in potentially adverse metabolic aberrations in children whose puberty is occurring at a physiologically normal time.<sup>57-59</sup> The emergence of AIs as a possible alternative means of delaying epiphyseal fusion and prolonging linear growth has, therefore, generated immense interest. Before widespread acceptance, it is critical to examine the existing data on use of AIs in boys with short stature with an emphasis on its limitations and the remaining questions.

The literature regarding the use of AIs for treatment of boys with short stature is limited to a small number of original studies<sup>60-65</sup> and 2 reviews.<sup>4,66</sup> The primary data from the 6 English-language articles cited in PubMed are summarized in Table 2. Taken together, these data suggest that AIs hold promise for increasing adult height in short children, apparently by maintaining growth velocity while decreasing bone age progression. Although limited to 1 report,<sup>65</sup> the available data on near adult height indicate that gains noted during initial therapy may be (although not always fully) sustained into adulthood.

Several features are common among the published reports. All of the data derive from interventions limited to male patients (1 abstract reported treatment of female patients<sup>67</sup>), and the AIs used (anastrozole and letrozole) seemed to be well tolerated. When measured, estradiol levels were substantially decreased, whereas testosterone, follicle-stimulating hormone, and luteinizing hormone levels were significantly increased in those who received treatment compared with control subjects. Presumably, the increased follicle-stimulating hormone levels were primarily responsible for the increases in testicular volume noted during initial treatment in 2 of the trials.<sup>61,64</sup> The effects of the high testosterone levels have not been systematically evaluated, but it is important to note that these levels may be substantially elevated and can reach values far above the adult male reference range. The highest levels were reported in the trial that involved patients with constitutional delay of growth and puberty, in which mean testosterone levels reached 1416 ng/dL (49.1 nmol/L) and 1863 ng/dL (64.6 nmol/L) in the initial treatment group and in the subgroup that was followed to near-adult height, respectively.<sup>61,65</sup> These values compare to control values of 456 ng/dL (15.6 nmol/L) and 542 ng/dL (18.8 nmol/L). Other features of the reports include some patients' experiencing gynecomastia while receiving the AIs,<sup>61</sup> which, along with reduced but still measurable levels of estradiol, indicates that none of the protocols likely achieved full blockade of aromatase enzyme activity. In each report, the hormonal changes that were induced by the AIs all normalized within 6 months after the discontinuation of treatment.<sup>60,61,64</sup> Finally, growth velocity seems to have been preserved in the treatment groups despite apparent lack of estradiol-induced changes in insulin-like growth factor-1 levels during treatment.<sup>61,62</sup>

**TABLE 2 Studies Evaluating the Effect of AIs on Growth in Boys With Short Stature**

Reference	Study Type	No. of Subjects	Underlying Diagnoses	Mean CA, y	Mean BA, y	Treatment Protocol	Outcome
Faglia et al <sup>60</sup> , 2000	Case Report	1	History of central precocious puberty	11.0	16.4	Anastrozole 1.0 mg orally once daily for 36 mo during endogenous puberty	Gain of 6 cm over pretherapy predicted height; BA progressed only 19 mo during 36 mo
Wickman et al <sup>61</sup> , 2001	RDBPCT	22 (10 therapy; 12 placebo)	Constitutional delay	15.2 therapy; 15.0 placebo	13.1 therapy; 12.6 placebo	T enanthate 1 mg/kg every 4 weeks × 6 plus letrozole 2.5 mg once daily or placebo for 12 mo	Mean increase in predicted adult height of 5.1 ± 3.7 cm letrozole versus placebo
Mauras et al <sup>62</sup> , 2004	Open label, controlled, not an RDBPCT	19 (10 therapy; 9 control)	Growth hormone deficiency	14.9 therapy; 15.1 control	13.2 therapy; 13.4 control	Growth hormone 0.3 mg/kg per wk plus anastrozole 1 mg once daily or no therapy for 12 mo	No difference in GV, height SDS, BA advancement, or predicted adult height in therapy versus control group
Karmazin et al <sup>63</sup> , 2005	Chart review	24	Various; 6 different diagnoses included; 15 of 24 on GH therapy, 6 of 24 on androgen therapy	14.0	Not reported	Letrozole 2.5 mg once daily for mean of 12.3 mo plus ongoing other therapy	Predicted height SDS increase 0.77 (no androgen therapy) and 1.03 (androgen therapy); BA progression decelerated; GV did not change
Hero et al <sup>64</sup> , 2005	RDBPCT	30 (16 therapy; 14 placebo)	Idiopathic short stature, including SGA	11.0 therapy; 11.0 placebo	9.1 therapy; 8.9 placebo	Letrozole 2.5 mg once daily or placebo for 24 mo	Predicted height increase 5.9 cm; height SDS for BA increase 0.7; BA progression decelerated; no difference seen in GV
Hero et al <sup>65</sup> , 2006	RDBPCT, follow-up of previous study <sup>2</sup>	17 (9 therapy; 8 placebo), final data from 3 fewer than in previous study <sup>2</sup>	Constitutional delay	15.2 therapy; 14.8 placebo	Delayed; 2.2 therapy; 2.3 placebo	T enanthate, 1 mg/kg every 4 weeks × 6 plus letrozole 2.5 mg once daily or placebo for 12 mo (as in previous study <sup>2</sup> ) followed to near final height	Near final height closer to MPH in therapy versus placebo group, -1.3 vs -4.8 cm; 0.6 SDS additional increase in height compared with pretherapy height in therapy group

CA, chronological age; BA, bone age; RDBPCT, randomized, double-blind, placebo-controlled trial; SDS, SD score; GV, growth velocity; SGA, small for gestational age; T, testosterone; MPH, midparental height.

Although these reports are encouraging, it is important that they be interpreted cautiously. In the combined reports, only 61 patients had been treated, and only 2 randomized, double-blinded, placebo-controlled trials had been performed. Three of the 6 original reports derive from the same research group,<sup>61,64,65</sup> and 2 of those involve the same initial patients.<sup>61,65</sup> Only 9 patients have been followed to near-adult height; there are no available data regarding adult heights from the controlled trials. Moreover, 1 of the studies involving patients with growth hormone deficiency found no change in mean predicted adult height among the patients who were treated with the AI.<sup>62</sup>

The reasons for the lack of effect in this study of growth hormone-deficient boys are not clear. Theoretically, it could stem from less effective blockade of enzyme activity by anastrozole than letrozole or from too short an intervention (12 months). Alternatively, this study could be an indication that there are important limitations in the ability of AIs to increase adult height. In support of the first hypotheses is a related ongoing randomized, double-blinded, placebo-controlled trial reported thus far only in abstract form.<sup>68</sup> This trial involves 52 growth hormone-deficient boys who were randomly assigned to receive growth hormone or growth hormone plus anastrozole and has thus far demonstrated an increase in predicted adult height of 2 cm in those who received the AI for 24 months. Conversely, the possibility of limitations on efficacy is supported by another abstract<sup>69</sup> reporting 2 years of data from an open-label study involving 40 boys with idiopathic short stature, 20 of whom received anastrozole for 2 years. In this study, treatment seemed neither to slow skeletal maturation nor to increase predicted adult height. Similarly, it should be noted that 3 patients in 1 of the published reports experienced an increase in progression of bone age compared with chronologic age<sup>63</sup> and that 1 patient in another report experienced a decrease in predicted adult height of 3.5 cm while on therapy.<sup>61</sup>

Although the overall results of treatment with AIs are encouraging and their use seems to be rapidly expanding, we agree with the recommendation by several of the authors of the above-mentioned studies that endocrinologists should be cautious and that AIs should preferentially be used within carefully controlled clinical trials.<sup>60-65</sup> More data on adult heights are needed. If AIs are shown to increase adult height, then questions that will still need to be addressed include the optimal agent and dosage, the duration of therapy, and whether the intervention is equally efficacious regardless of underlying diagnosis (eg, do patients with idiopathic short stature, constitutional delay of growth and maturation, and growth hormone deficiency all gain similarly?). What is the average and range of the gain in adult (not predicted adult) height? Are there predictors of height gain such as chronologic age or bone age at initiation of therapy? In 1 report, outcome did not depend on bone age at initiation, but the mean bone age at baseline was only  $9.1 \pm 2.3$  years.<sup>65</sup> It is not yet clear how effective the intervention would be among children with more advanced bone ages.

## SAFETY ISSUES

For short stature as well as other indications, it is critical that additional safety data be obtained during subsequent clinical trials. The available short-term data are reassuring; however, long-term data are lacking, and the number of children and adolescents who are treated within trials is still small. These safety concerns are perhaps most pertinent to short stature, for which the number of youth who might be treated is large. An area of substantial concern is the potential effect on bone mineral density (BMD) of a treatment regimen that decreases estradiol concentrations. Although data are limited, BMD of lumbar vertebrae, the femoral neck, and whole body as well as markers of bone formation, such as alkaline phosphatase and osteocalcin, have been assessed in several of the published reports.<sup>61,62,64</sup> The available data are reassuring and indicate that as puberty progressed, bone density increased similarly in patients who were receiving AIs and in control subjects, and 1 study even reported that volumetric, as opposed to areal, BMD of the lumbar spine increased during AI administration.<sup>64</sup> Although the ability to preserve and perhaps even temporarily advance<sup>62,64</sup> the progression of puberty in boys is an attractive feature of AIs, potential effect on spermatogenesis and sperm motility is another area of concern.<sup>70,71</sup> This issue has not yet been fully assessed in children and adolescents who are treated with AIs,<sup>72</sup> and it is imperative that normal spermatogenesis be verified in larger studies with longer follow-up. Related to other safety concerns, Hero et al<sup>73</sup> reported that aromatase inhibition reduced high-density lipoprotein cholesterol and decreased relative fat mass in boys who were treated for 2 years, but no significant effects on insulin sensitivity have been observed.

Acquisition of additional data regarding bone health, reproductive function, lipid and carbohydrate metabolism, and adrenal function will be important in assessing the pros and cons of AI therapy. These additional safety data are critical to providing sufficient surveillance for relatively rare adverse effects that might influence the clinical use of these agents but have not yet been detected among the small number of patients studied to date.

## CONCLUSIONS

The use of third-generation AIs will likely play an emerging role in the treatment of specific endocrine disorders in children. They are well tolerated and are available as a convenient once-daily oral dose; however, safety information regarding long-term effects of AIs on indices such as bone mineral acquisition, spermatogenesis, and exposure to supraphysiologic testosterone levels are still needed. In addition, definitive data for most indications are still lacking. AIs when combined with antiandrogens are the treatment of choice for male limited peripheral precocious puberty, and data from an ongoing clinical trial may provide additional evidence in support of the specific combination of bicalutamide with anastrozole. Use of similar combined therapy as an adjunct to traditional therapy for CAH, allowing lower glucocorticoid dosages, may prove effective to increase

adult height and prevent early virilization; results of a long-term study testing this hypothesis should be forthcoming. Efficacy of AIs in girls with MAS seems to be limited; progression of ovarian cyst formation may further curtail utility in this group of patients. Use of AIs in boys with idiopathic short stature and short stature associated with growth hormone deficiency or constitutional delay may increase adult height modestly; however, data on adult height are lacking, and there is no information identifying which children are likely to benefit most. Additional controlled studies are required before this therapy can be routinely recommended to augment adult height. There is no current evidence that third-generation AIs reduce pubertal gynecomastia; studies testing the hypothesis that benefit would derive from initiating therapy before 6 months and establishing a more effective blockade need to be performed. Thus, despite the potential promise of these agents in the treatment of selected pediatric endocrine disorders, we urge physicians to exercise caution in the use of these agents outside of controlled clinical trials.

#### ACKNOWLEDGMENTS

We thank members of the Lawson Wilkins Pediatric Endocrine Society (LWPES) Drug and Therapeutics Committee, Drs Madhusmita Misra, Daniele Pacaud, Anna Petryk, Paulo Solberg, and Phyllis Speiser, and LWPES Secretary Dr Alan Rogol for valuable input in the preparation of this manuscript. We also thank members of the LWPES membership at large who provided useful commentary.

#### REFERENCES

- Brodie AM, Banks PK, Inkster SE, Dowsett M, Coombes RC. Aromatase inhibitors and hormone dependent cancers. *J Steroid Biochem Mol Biol*. 1990;37(3):327-333
- Bulun SE, Zeitoun K, Takayama K, et al. Estrogen production in endometriosis and use of aromatase inhibitors to treat endometriosis. *Endocr Relat Cancer*. 1999;6(2):293-301
- Miller WR, Jackson J. The therapeutic potential of aromatase inhibitors. *Expert Opin Investig Drugs*. 2003;12(3):337-351
- Dunkel L. Use of aromatase inhibitors to increase final height. *Mol Cell Endocrinol*. 2006;254-255:207-216
- Plourde PV, Reiter EO, Jou H-C, et al. Members of the Asra-Zeneca Gynecomastia Study. Safety and efficacy of anastrozole for the treatment of pubertal gynecomastia: a randomized, double-blind, placebo-controlled trial. *J Clin Endocrinol Metab*. 2004;89(9):4428-4433
- Smith EP, Boyd J, Frank GR, et al. Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. *N Engl J Med*. 1994;331(16):1056-1061
- Morishima A, Grumbach M, Simpson E, Fisher C, Qin K. Aromatase deficiency in male and female siblings caused by a novel mutation and the physiological role of estrogens. *J Clin Endocrinol Metab*. 1995;80(12):3689-3698
- Cash R, Brough AJ, Cohen MN, Satoh PS. Aminoglutethimide (Elipten-Ciba) as an inhibitor of adrenal steroidogenesis: mechanism of action and therapeutic trial. *J Clin Endocrinol Metab*. 1967;27(9):1239-1248
- Thompson EA Jr, Siiteri PK. The involvement of human placental microsomal cytochrome P-450 in aromatization. *J Biol Chem*. 1974;249(17):5373-5378
- Geisler J, Lonning PE. Aromatase inhibition: translation into a successful therapeutic approach. *Clin Cancer Res*. 2005;11(8):2809-2821
- Cavalli A, Bisi A, Bertucci C, et al. Enantioselective nonsteroidal aromatase inhibitors identified through a multidisciplinary medicinal chemistry approach. *J Med Chem*. 2005;48(23):7282-7289
- Numazawa M, Handa W, Hasegawa C, Takahashi M. Structure-activity relationships of 2 alpha-substituted androstenedione analogs as aromatase inhibitors and their aromatization reactions. *J Steroid Biochem Mol Biol*. 2005;97(4):353-359
- Cavaliere E, Chakravarti D, Guttenplan J, et al. Catechol estrogen quinones as initiators of breast and other human cancers: implications for biomarkers of susceptibility and cancer prevention. *Biochem Biophys Acta*. 2006;1766(1):63-78
- Chen S, Zhang F, Sherman MA, et al. Structure-function studies of aromatase and its inhibitors: a progress report. *J Steroid Biochem Mol Biol*. 2003;86(3-5):231-237
- Saber MR, Vinh TK, Yee SW, Griffiths BJ, Evans PJ, Simons C. CYP19 (aromatase) 1-[(benzofuran-2-yl)(phenylmethyl)pyridine, -imidazole, and -triazole inhibitors: synthesis and biological evaluation. *J Med Chem*. 2006;49(3):1016-1022
- Walgreens.com. Drug Information. Available at [www.walgreens.com/library/finddrug/druginfosearch.jsp](http://www.walgreens.com/library/finddrug/druginfosearch.jsp). Accessed February 4, 2008.
- Eugster EA. Aromatase inhibitors in precocious puberty: rationale and experience to date. *Treat Endocrinol*. 2004;3(3):141-151
- Geisler J, Lonning PE. Endocrine effects of aromatase inhibitors and inactivators in vivo: review of data and method limitations. *J Steroid Biochem Mol Biol*. 2005;95(1-5):75-81
- Laue L, Kenigsberg D, Pescovitz OH, et al. Treatment of familial male precocious puberty with spironolactone and testolactone. *N Engl J Med*. 1989;320(8):496-502
- Laue L, Jones J, Barnes KM, Cutler GB Jr. Treatment of familial male precocious puberty with spironolactone, testolactone, and deslorelin. *J Clin Endocrinol Metab*. 1993;76(1):151-155
- Leschek EW, Jones J, Barnes KM, Hill SC, Cutler GB Jr. Six-year results of spironolactone and testolactone treatment of familial male-limited precocious puberty with addition of deslorelin after central puberty onset. *J Clin Endocrinol Metab*. 1999;84(1):175-178
- Reiter EO, Narjawaara E. Testotoxicosis: current viewpoint. *Pediatr Endocrinol Rev*. 2005;3(2):77-86
- Kreher NC, Pescovitz OH, Delameter P, Tiulpakov A, Hochberg Z. Treatment of familial male-limited precocious puberty with bicalutamide and anastrozole. *J Pediatr*. 2006;149(3):416-420
- Feuillan PP, Foster CM, Pescovitz OH, et al. Treatment of precocious in the McCune-Albright syndrome with the aromatase inhibitor testolactone. *N Engl J Med*. 1986;315(18):1115-1119
- Feuillan PP, Jones J, Cutler GB Jr. Long-term testolactone therapy for precocious puberty in girls with the McCune-Albright syndrome. *J Clin Endocrinol Metab*. 1993;77(3):647-651
- Nunez SB, Calis K, Cutler GB Jr, Jones J, Feuillan PP. Lack of efficacy of fadrozole in treating precocious puberty in girls with the McCune-Albright syndrome. *J Clin Endocrinol Metab*. 2003;88(12):5730-5733
- Roth C, Freiberg C, Zappel H, Albers N. Effective aromatase inhibition by anastrozole in a patient with gonadotropin-independent precocious puberty in McCune-Albright syndrome. *J Pediatr Endocrinol Metab*. 2002;15(suppl 3):945-948
- Kunz GJ, Mao CS, Gottschalk ME. Anastrozole Use During Precocious Puberty in McCune-Albright Syndrome [abstract]. Presented at: 85th annual meeting of the Endocrine Society; June 19-20, 2003; Philadelphia, PA
- Mieszczyk J, Lowe E, Plourde P, Eugster EA. Anastrozole treat-



- ment of precocious puberty in girls with McCune-Albright syndrome [abstract 7517.7]. Presented at: annual meeting of the Pediatric Academic Society, May 3–8, 2007; Toronto, Ontario, Canada
30. Feuillan P, Calis K, Hill S, Shawker T, Robey PG, Collins MT. Letrozole treatment of precocious puberty in girls with the McCune-Albright syndrome: a pilot study. *J Clin Endocrinol Metab.* 2007;92(6):2100–2106
  31. Albers N, Jorgens S, Deiss D, Hauffa BP. McCune-Albright syndrome: the German experience. *J Pediatr Endocrinol Metab.* 2002;15(suppl 3):897–901
  32. Bonfig W, Bechtold S, Schmidt H, Knorr D, Schwarz HP. Reduced final height outcome in congenital adrenal hyperplasia under prednisone treatment: deceleration of growth velocity during puberty. *J Clin Endocrinol Metab.* 2007;92(5):1635–1639
  33. Silva IN, Kater CE, Cunha CF, Viana MB. Randomised controlled trial of growth effect of hydrocortisone in congenital adrenal hyperplasia. *Arch Dis Child.* 1997;77(3):214–218
  34. Eugster EA, Dimeglio LA, Wright JC, Freidenberg GR, Seshadri R, Pescovitz OH. Height outcome in congenital adrenal hyperplasia caused by 21-hydroxylase deficiency: a meta-analysis. *J Pediatr.* 2001;138(1):26–32
  35. Merke DP, Keil MF, Jones JV, Fields J, Hill S, Cutler GB Jr. Flutamide, testosterone, and reduced hydrocortisone dose maintain normal growth velocity and bone maturation despite elevated androgen levels in children with congenital adrenal hyperplasia. *J Clin Endocrinol Metab.* 2000;85(3):1114–1120
  36. Braunstein G. Gynecomastia. *N Engl J Med.* 1993;328(7):490–495
  37. Harlan WR, Grillo GP, Cornoni-Huntley J, Leaverton PE. Secondary sex characteristics of boys 12 to 17 years of age: the U.S. Health Examination Survey. *J Pediatr.* 1979;95(2):293–297
  38. Williams M. Gynecomastia: Its incidence, recognition and host characterization in 447 autopsy cases. *Am J Med.* 1963;34:103–112
  39. Nicolis GL, Modlinger RS, Gabrilove JL. A study of the histopathology of human gynecomastia. *J Clin Endocrinol Metab.* 1971;32(2):173–178
  40. Bannayan GA, Hajdu SI. Gynecomastia: clinicopathologic study of 351 cases. *Am J Clin Pathol.* 1972;57(4):431–437
  41. Nydick M, Bustos J, Dale JH Jr, Rawson RW. Gynecomastia in adolescent boys. *JAMA.* 1961;178:449–454
  42. Plourde P, Julin H, Santner S. Clomiphene in the treatment of adolescent gynecomastia. *Am J Dis Child.* 1983;137(11):1080–1082
  43. König R, Schonberger W, Neumann P, Benes P, Grimm W. Treatment of marked gynecomastia in puberty with tamoxifen [in German]. *Klin Padiatr.* 1987;199(6):389–391
  44. Eberle A, Sparrow J, Keenan B. Treatment of persistent pubertal gynecomastia with dihydrotestosterone heptanoate. *J Pediatr.* 1986;109(1):144–149
  45. Beck W, Stubbe P. Endocrinological studies of the hypothalamo-pituitary gonadal axis during danazol treatment in pubertal boys with marked gynecomastia. *Horm Metab Res.* 1982;14(12):653–657
  46. Zachmann M, Eiholzer U, Muritano M, Werder EA, Manella B. Treatment of pubertal gynecomastia with testosterone. *Acta Endocrinol.* 1986;279(suppl):218–226
  47. Riepe FG, Baus I, Wiest S, Krone N, Sippell WG, Partsch CJ. Treatment of pubertal gynecomastia with the specific aromatase inhibitor anastrozole. *Horm Res.* 2004;62(3):113–118
  48. Klein KO, Baron J, Colli MJ, McDonnell DP, Cutler GB Jr. Estrogen levels in childhood determined by an ultrasensitive recombinant cell bioassay. *J Clin Invest.* 1994;94(6):2475–2480
  49. Boccardo F, Rubagotti A, Battaglia M, et al. Evaluation of tamoxifen and anastrozole in the prevention of gynecomastia and breast pain induced by bicalutamide monotherapy of prostate cancer. *J Clin Oncol.* 2005;23(4):808–815
  50. Lefevre H, Bouvattier C, Lahlou N, Adamsbaum C, Bougneres P, Carel J-C. Prepubertal gynecomastia in Peutz-Jeghers syndrome: incomplete penetrance in a familial case and management with an aromatase inhibitor. *Eur J Endocrinol.* 2006;154(2):221–227
  51. Kara C, Kutlu AO, Tosun MS, Apaydin S, Senel F. Sertoli cell tumor causing prepubertal gynecomastia in a boy with Peutz-Jeghers syndrome: the outcome of 1 year treatment with the aromatase inhibitor testosterone. *Horm Res.* 2005;63(5):252–256
  52. Shozu M, Sebastian S, Takayama K, et al. Estrogen excess associated with novel gain-of-function mutations affecting the aromatase gene. *N Engl J Med.* 2003;348(19):1855–1865
  53. Stratakis CA, Vottero A, Brodie A, et al. The aromatase excess syndrome is associated with feminization of both sexes and autosomal dominant transmission of aberrant P450 aromatase gene transcription. *J Clin Endocrinol Metab.* 1998;83(4):1348–1357
  54. Leschek EW, Rose SR, Yanovski JA, et al. Effect of growth hormone treatment on adult height in peripubertal children with idiopathic short stature: a randomized, double-blind, placebo-controlled trial. *J Clin Endocrinol Metab.* 2004;89(7):3140–3148
  55. Wit JM, Balen HV, Kamp GA, Oostdijk W. Benefit of postponing normal puberty for improving final height. *Eur J Endocrinol.* 2004;151(suppl 1):S41–S45
  56. Pasquino AM, Pucarelli I, Roggini M, Segni M. Adult height in short normal girls treated with gonadotropin-releasing hormone analogs and growth hormone. *J Clin Endocrinol Metab.* 2000;85(2):619–622
  57. Mauras N, Hayes V, Welch S, et al. Testosterone deficiency in young men: marked alterations in whole body protein kinetics, strength, and adiposity. *J Clin Endocrinol Metab.* 1998;83(6):1886–1892
  58. Boot AM, Demuinck Keizer-Schrama SM, Pols HA, Drenning EP, Drop SL. Bone mineral density and body composition before and during treatment with gonadotropin-releasing hormone agonist in children with precocious and early puberty. *J Clin Endocrinol Metab.* 1998;83(2):370–373
  59. Yanovski JA, Rose SR, Municchi G, et al. Treatment with a luteinizing hormone-releasing hormone agonist in adolescents with short stature. *N Engl J Med.* 2003;348(10):908–917
  60. Faglia G, Arosio M, Porretti S. Delayed closure of epiphyseal cartilages induced by the aromatase inhibitor anastrozole: would it help short children grow up? *J Endocrinol Invest.* 2000;23(11):721–723
  61. Wickman S, Sipila I, Ankarberg-Lindgren C, Norjavaara E, Dunkel L. A specific aromatase inhibitor and potential increase in adult height in boys with delayed puberty: a randomized controlled trial. *Lancet.* 2001;357(9270):1743–1748
  62. Mauras N, Welch S, Rini A, Klein KO. An open label 12-month pilot trial on the effects of the aromatase inhibitor anastrozole in growth hormone (GH)-treated GH deficient adolescent boys. *J Pediatr Endocrinol Metab.* 2004;17(12):1597–1606
  63. Karmazin A, Moore WV, Popovic J, Jacobson JD. The effect of letrozole on bone age progression, predicted adult height, and adrenal gland function. *J Pediatr Endocrinol Metab.* 2005;18(3):285–293
  64. Hero M, Norjavaara E, Dunkel L. Inhibition of estrogen biosynthesis with a potent aromatase inhibitor increases predicted adult height in boys with idiopathic short stature: a randomized controlled trial. *J Clin Endocrinol Metab.* 2005;90(12):6396–6402
  65. Hero M, Wickman S, Dunkel L. Treatment with the aromatase inhibitor letrozole during adolescence increases near-final height in boys with constitutional delay of puberty. *Clin Endocrinol (Oxf).* 2006;64(5):510–513

66. Cernich J, Jacobson JD, Moore WV, Popovic J. Use of aromatase inhibitors in children with short stature. *Pediatr Endocrinol Rev.* 2004;2(1):2-7
67. Turpin AL, Popovic J, Karmazin A, Moore WV, Jacobson JD. Aromatase inhibitor may delay skeletal maturation and improve final adult height in females [abstract]. 86th Annual Meeting of the Endocrine Society, New Orleans, LA, June 16-19, 2004
68. Mauras N, Gonzalez de Pijem L, Hsiang H, et al. Placebo controlled, double blind, randomized trial of the safety and efficacy of Arimidex in delaying epiphyseal fusion in growth hormone (GH) deficient males in puberty: preliminary results [abstract]. 88th Annual Meeting of the Endocrine Society, Boston, MA, June 24-28, 2006
69. Front H, Lampit M, Hochberg Z. Aromatase inhibition therapy in pubertal short boys [abstract]. ESPE/LWPES Seventh Joint Meeting, Lyon, France, September 21-24, 2005
70. Carreau S, Delalande C, Silandre D, Bourquiba S, Lambard S. Aromatase and estrogen receptors in male reproduction. *Mol Cell Endocrinol.* 2006;246(1-2):65-68
71. Simpson ER. Genetic mutations resulting in estrogen insufficiency in the male. *Mol Cell Endocrinol.* 1998;145(1-2):55-59
72. Mauras N, Bell J, Snow BG, Winslow KL. Sperm analysis in growth hormone-deficient adolescents previously treated with an aromatase inhibitor: comparison with normal controls. *Fertil Steril.* 2005;84(1):239-242
73. Hero M, Ankarberg-Lindgren C, Taskinen MR, Dunkel L. Blockade of oestrogen biosynthesis in peripubertal boys: effects on lipid metabolism, insulin sensitivity, and body composition. *Eur J Endocrinol.* 2006;155(3):453-460

## Use of Aromatase Inhibitors in Children and Adolescents With Disorders of Growth and Adolescent Development

Dorothy I. Shulman, Gary L. Francis, Mark R. Palmert, Erica A. Eugster and for the Lawson Wilkins Pediatric Endocrine Society Drug and Therapeutics Committee

*Pediatrics* 2008;121:e975-e983

DOI: 10.1542/peds.2007-2081

<b>Updated Information &amp; Services</b>	including high-resolution figures, can be found at: <a href="http://www.pediatrics.org/cgi/content/full/121/4/e975">http://www.pediatrics.org/cgi/content/full/121/4/e975</a>
<b>References</b>	This article cites 66 articles, 33 of which you can access for free at: <a href="http://www.pediatrics.org/cgi/content/full/121/4/e975#BIBL">http://www.pediatrics.org/cgi/content/full/121/4/e975#BIBL</a>
<b>Citations</b>	This article has been cited by 1 HighWire-hosted articles: <a href="http://www.pediatrics.org/cgi/content/full/121/4/e975#otherarticles">http://www.pediatrics.org/cgi/content/full/121/4/e975#otherarticles</a>
<b>Subspecialty Collections</b>	This article, along with others on similar topics, appears in the following collection(s): <b>Therapeutics &amp; Toxicology</b> <a href="http://www.pediatrics.org/cgi/collection/therapeutics_and_toxicology">http://www.pediatrics.org/cgi/collection/therapeutics_and_toxicology</a>
<b>Permissions &amp; Licensing</b>	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="http://www.pediatrics.org/misc/Permissions.shtml">http://www.pediatrics.org/misc/Permissions.shtml</a>
<b>Reprints</b>	Information about ordering reprints can be found online: <a href="http://www.pediatrics.org/misc/reprints.shtml">http://www.pediatrics.org/misc/reprints.shtml</a>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

