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Free Drug Samples in the United States: Characteristics of Pediatric Recipients and Safety Concerns

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Abstract

OBJECTIVES—Free drug samples frequently are given to children. We sought to describe characteristics of free sample recipients, to determine whether samples are given primarily to poor and uninsured children, and to examine potential safety issues.

METHODS—We analyzed data on 10 295 US residents <18 years of age from the 2004 Medical Expenditure Panel Survey, a nationally representative survey that includes questions on receipt of free drug samples. We performed bivariate and multivariate analyses to evaluate characteristics associated with receipt of ≥1 free drug sample in 2004. We identified the most frequently reported sample medications and reviewed potential safety issues.

RESULTS—Ten percent of children who received prescription medications and 4.9% of all children received ≥1 free drug sample in 2004. In bivariate analyses, poor children (family incomes of <200% of the federal poverty level) were no more likely to receive free samples than were those with incomes of ≥400% of the poverty level (3.8% vs 5.9%). Children who were uninsured for part or all of the year were no more likely to receive free samples than were those who were insured all year (4.5% vs 5.1%); 84.3% of all sample recipients were insured. In multivariate analyses, routine access to health care (≥3 provider visits in 2004) was associated with free sample receipt. The 15 most frequently distributed pediatric free samples in 2004 included 1 schedule II controlled medication, Adderall (amphetamine/dextroamphetamine), and 4 medications that received new or revised black box warnings between 2004 and 2007, Elidel (pimecrolimus), Advair (fluticasone/salmeterol), Strattera (atomoxetine), and Adderall (amphetamine/dextroamphetamine).

CONCLUSIONS—Poor and uninsured children are not the main recipients of free drug samples. Free samples do not target the neediest children selectively, and they have significant safety considerations.

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What's Known on This Subject
Although the use of free samples by adults has received increasing national attention, little is known about free sample distribution in pediatric populations.

What This Study Adds
We describe factors associated with free sample receipt in a pediatric population and identify potential safety concerns associated with free samples.

Keywords

free drug samples; drug safety; medically underserved; access to health care; black box warning; uninsured; drug packaging; health insurance

Although the use of free drug samples by adults has received increasing national attention,[1–4] little is known about free sample distribution in pediatric populations. Studies of free sample use among adults have addressed safety concerns,[5–6] health professionals' diversion of samples for self-administration or resale,[7–9] and the contribution of samples to increasing drug costs.[2,10] In addition, numerous adult studies suggest that free samples influence the prescribing behavior of physicians and trainees.[2,9–15] Physicians alter their prescribing patterns when using samples, choosing medications that are more expensive,[2] less likely to be first-line agents,[11] and less likely to be consistent with the physicians' own, self-described, prescribing preferences.[10] In a recent report, the Institute of Medicine called for further investigation of sample use.[16] Concerns cited in the report include the lack of documentation of sample medications and the bypassing of standard prescribing and dispensing services, including counseling and drug interaction checks.

Free sample distribution seems to be common in pediatric populations. A national survey of physicians published in 2007 found that 78% of physicians reported receiving drug samples for their patients; more than one third of respondents to that survey were either pediatricians or family practitioners.[17] Information on the safety of free samples for children is limited. Samples often have inadequate or absent labeling regarding pediatric dosing.[6] Child-resistant packaging (or warnings that the packaging is not child-resistant), instructions to keep the drug out of the reach of children, and instructions on seeking advice in the case of accidental overdose also are absent for a large proportion of samples.[6] Moreover, sample distribution removes a layer of redundancy in prescribing (ie, pharmacist review and instructions before the first dose), which may allow physician and patient errors to go unnoticed.

Despite safety and prescribing concerns, samples have several potential benefits. Samples can be a convenient way to test a flavor or preparation to determine whether a child will tolerate the medicine, before the prescription is filled. Samples may be used to establish goodwill or to form a bond between a health care practitioner and a patient or parent. In addition, many physicians describe free samples as a valuable way to provide medications to needy patients.[18] This view is espoused by the Pharmaceutical Research and Manufacturers of America, whose vice president wrote, "Many uninsured and low-income patients benefit from these free samples, which often serve as a safety net."[19]

No national study has described characteristics of pediatric free sample recipients. We examined factors associated with free sample receipt in a pediatric population by using nationally representative data for 2004. We investigated whether samples were given primarily to poor and uninsured children, we characterized the medications most frequently sampled, and we identified safety concerns associated with those medications.

METHODS

Data Source

We analyzed the Agency for Healthcare Research and Quality 2004 Medical Expenditure Panel Survey (MEPS), Household Component, limiting our analysis to respondents <18 years of age as of December 31, 2004. The MEPS is a nationally representative, longitudinal survey of the civilian, noninstitutionalized, US population. The MEPS cohort is drawn from respondents to the previous year's National Health Interview Survey (NHIS), conducted by the National

Center for Health Statistics of the Centers for Disease Control and Prevention. The NHIS uses a stratified, multistage, probability cluster sampling design with oversampling of black and Hispanic subjects.[20]

MEPS surveyors query respondents 5 times over a total of 2.5 years. Interviewers travel to the homes of respondents and conduct in-person, computer-assisted interviews with a single respondent for each household. The respondent is intended to be the person with the most knowledge about the family's health care. Most children are not interviewed directly. For students living at school, however, contact information is obtained from the parents and interviews are conducted directly with the student.

The MEPS collects detailed information on health care expenditures, health care utilization (including hospitalizations, outpatient visits to health care providers, and visits to rehabilitation specialists), health insurance, and sociodemographic characteristics, as well as information on all outpatient medications. The MEPS is considered a complete source of data on the cost and use of health care and health insurance coverage. The Agency for Healthcare Research and Quality provides weights that adjust for the complex sampling design and survey nonresponse and allow extrapolation to the US population as a whole. MEPS data are deidentified and are nationally available online. This study was reviewed by the institutional review board of Cambridge Health Alliance and was considered "minimal risk" due to the use of deidentified, nationally available data.

Identification of Samples Received

In every interview, MEPS surveyors ask participants to name all filled prescriptions received in conjunction with a hospital discharge, emergency department visit, or medical outpatient visit. Surveyors then ask respondents to name any medications purchased or received that have not already been listed. The surveyor then asks, "Since [the last interview], did [you] get any free samples of prescribed medicines from a medical or dental provider that we have not yet talked about?" The MEPS defines free samples as "limited amounts of a prescription medication which are given out by doctors to patients free of charge, sometimes in lieu of a written or verbal prescription." If a respondent answers yes to this question, then the names of any medicines received as samples are obtained.

Statistical Analyses

We analyzed bivariate associations between receipt of ≥1 free sample in 2004 and family income (as a percentage of the poverty level) and also bivariate associations between receipt of ≥1 free sample and insurance status. We conducted similar bivariate analyses examining various demographic characteristics, including the age of the child by the end of 2004, gender, race/ethnicity, and language spoken. Because we used the age of the child as of December 31, 2004, we might have slightly overestimated the child's age at the time of sample receipt. In addition, we conducted bivariate analyses looking at health care access-related characteristics, including site of primary medical care, number of visits to a medical or dental provider in 2004, and number of medications received in 2004. Each refill was counted as a separate medication event.

Next, we examined the impact of demographic and access-related variables on the relationships between free drug sample receipt and insurance status and income. We developed a multivariate logistic regression model by using the same definitions for outcome, insurance classification, and income category as used in the bivariate models. We analyzed the impact of insurance and income on free sample receipt while controlling for demographic features, including age, gender, and race/ethnicity. We then created a second model by adding access-related variables.

To identify potential safety issues associated with pediatric free sample use, we reviewed the names of sample medications received by children in the MEPS. We identified the 15 most frequently named medications and then used weights provided by the MEPS to estimate the number of pediatric recipients for these medications nationwide. We present these 15 sample medications ranked according to national population figures, and we also present the median age of pediatric recipients for each medication. We then reviewed the Food and Drug Administration Web site and medication labels in the *Physicians' Desk Reference* for the 15 most commonly distributed sample medications. We classified samples as having clinically relevant safety concerns if (1) there was a black box warning relevant to pediatric populations at the time of sample distribution, (2) a black box warning was added or revised after the date of sample distribution, (3) the drug was a schedule II controlled substance, or (4) a contraindication for use in pediatric populations was listed. Extending our review, we identified several sample medications that were not among the top 15 but also had significant safety concerns.

We were able to determine the number of children who received ≥1 free sample of a particular medication. Because the MEPS does not ask how many pills each sample contained, we cannot report an exact count of the number of pills received as free samples.

Statistical Methods

We calculated the number of children receiving free samples in 2004 as a proportion of all children and as a proportion of all children taking ≥1 prescription drug. We used χ^2 tests to examine the association between categorical predictors and free drug sample receipt. We used SAS 9.1 (SAS Institute, Cary, NC) and adjusted the confidence intervals (CIs) to account for the complex survey design.

We constructed our principal multivariate model of predictors of sample receipt by including insurance and income in the model, along with age, gender, and race/ethnicity. Because we considered it likely that variables measuring health care access were on the causal pathway to free drug sample receipt, we chose not to include them in our principal model. Rather, we constructed a second, exploratory model, including all of the aforementioned demographic variables and adding 3 variables related to health care access, that is, the number of prescription medications received in 2004 (each refill was counted as a separate medication event), the site of primary medical care (office-based, hospital clinic, or emergency department, no usual provider), and the number of visits to a medical or dental provider in 2004.

RESULTS

Impact of Insurance and Income on Free Drug Sample Receipt

Ten percent of children who received prescription medications and 4.9% of all US children received ≥1 free drug sample in 2004. Table 1 displays the characteristics of sample recipients. Neither income nor insurance status was a significant predictor of sample receipt, although poor children were slightly less likely to receive free samples (3.8% of low-income children), compared with middle-income (5.4%) or higher-income (5.9%; $P = .237$) children. Similarly, children who were uninsured for part or all of the year were slightly less likely to receive free samples than were those who were continuously insured (4.5% of those uninsured for part or all of the year vs 5.1% of those insured all year; $P = .663$).

Of all children who received a sample, only 15.7% of sample recipients were uninsured for all or part of the year, whereas 84.3% were insured continuously. Similarly, 30.8% of sample recipients had family incomes <200% of the poverty level, whereas 69.2% had family incomes ≥200% of the federal poverty level.

Hispanic and nonwhite children were much less likely to receive free samples, compared with non-Hispanic white children (2.4% of Hispanic children and 3.5% of non-Hispanic nonwhite children vs 6.2% of non-Hispanic white children; $P < .001$). Free sample receipt was associated significantly with variables indicative of access to health care. Children who visited medical or dental providers more frequently, who used office-based primary care, and who received a greater number of medications in 2004 were all more likely to receive free samples.

Table 2 presents the results of our multivariate analyses of sample receipt. In our principal model, we analyzed income and insurance as predictors of free sample receipt, controlling for age, gender, and race/ethnicity. Children who were uninsured for part or all of the year were no more likely to receive free samples (odds ratio [OR]: 1.05; 95% CI: 0.78–1.42) than were those who were continuously insured. Children in the lowest income group were no more likely to receive free samples (OR: 0.78; 95% CI: 0.56–1.08) than were those in the highest income group.

Our exploratory model incorporated 3 measures of health care access along with the sociodemographic characteristics described above. Greater use of health care services was associated with greater odds of sample receipt. After controlling for health care access, children who were uninsured for part or all of the year seemed more likely to receive free samples (OR for sample receipt: 1.49; 95% CI: 1.08–2.05), compared with those who were insured. The association between low income and free sample receipt remained nonsignificant (OR: 0.90; 95% CI: 0.63–1.29).

Description of Sample Medications Most Frequently Received

As shown in Table 3, the 15 most frequently distributed pediatric drug samples included medications used to treat allergic and respiratory symptoms (8 medications), antibiotics (4 medications), medications used to treat attention-deficit/hyperactivity disorder (2 medications), and 1 medication used to treat atopic dermatitis. The median age of sample recipients ranged from 4 years for Augmentin (amoxicillin/clavulanate) to 12 years for both Strattera (atomoxetine) and Adderall (amphetamine/dextroamphetamine) and 13.5 years for Allegra (fexofenadine).

Safety Concerns

We identified significant safety concerns for 4 (27%) of the 15 most frequently distributed samples (Table 4). All 4 medications acquired new black box warnings or significant revisions to existing black box warnings between 2004 and 2006. For instance, the warning added to Elidel (pimecrolimus) in 2006 included the statement that use for children <2 years of age was not indicated. Our data indicated that as many as 38 185 children <2 years of age received this medication. In addition, 1 of the top 15 sample medications was a schedule II controlled substances.

DISCUSSION

Our study demonstrates that free samples are widely distributed to children and are associated with significant safety concerns. One in 20 US children received a free sample in 2004, and 1 of 10 using a prescription medication received a free sample that year. Neither income nor insurance status was a significant predictor of free sample receipt. Characteristics significantly associated with greater free sample receipt included white race/non-Hispanic ethnicity, a greater number of provider visits and a greater number of medications, supporting the conclusion that it is not financial need but rather access to medical care that is the primary mediator of free sample receipt.

After we controlled for health care access, we found that uninsured children seemed significantly more likely to receive free samples than continuously insured children. This apparent reversal of our univariate findings offers important insight into the controversy that surrounds free sample distribution. We think this finding reflects the sincere efforts of doctors to put free samples in the hands of needy children once those children arrive in the office. Despite such good intentions, however, system-wide barriers that prevent access to medical care prevent free samples from being targeted to the most disadvantaged children.

Although we know of no previous studies that focused on characteristics of pediatric free sample recipients, our findings regarding the role of access to medical care in free sample receipt are consistent with those of our previous study,[1] which analyzed free drug sample receipt in a nationally representative sample that included both adults and children. Our findings also are consistent with those of a recently published national physician survey.[17] Campbell et al[17] found that physicians in hospitals or clinics (who treat larger proportions of poor and uninsured patients) are far less likely than physicians in group or solo practice settings to be given samples from the pharmaceutical industry. Their study, like ours, found little relationship between a physician's free sample receipt and the proportion of patients with Medicaid coverage or without insurance in that physician's practice. Of note, compared with family practitioners, pediatricians were one half as likely to report receiving free samples (OR: 0.56; 95% CI: 0.33–0.94) for use in their practices.

If, as our study indicates, free samples fail to improve equality of medication access on a national scale, then their continued presence in family medicine and pediatric practices across the country may be difficult to justify. Moreover, samples have the potential to harm as well as to help. New medications frequently are released onto the market before their safety profile is fully understood,[21] and samples tend to be newer medications.[22] If samples influence provider prescribing, as many studies have indicated,[9–15] then the use of free samples may increase pediatric prescriptions for newer medications. Our study showed that, of the 15 medications most frequently distributed as free samples in 2004, 4 (27%) received new or revised black box warnings in the subsequent 2 years. Free samples may encourage the use of medications in children before enough is known about potential harm.

In addition, we found that several of the 15 most frequently distributed free samples were broad-spectrum antibiotics or medications not considered to be first-line therapy. Samples that encourage providers to prescribe newer and broader-spectrum antibiotics exacerbate antibiotic misuse and may contribute directly to increased antimicrobial resistance.

Our finding that 1 of the top 15 sample medications was a schedule II controlled substance raises other safety concerns. Personal and unsupervised use of free samples by doctors, nurses, office staff members, and pharmaceutical representatives is common.[8,9,23] Occasionally, even patients may have unsupervised access to office sample closets.[5] Even in less drastic situations, the informality of free sample distribution may inadvertently communicate a lax attitude toward medication risks. Physicians, nurses, or office staff members may distribute free samples to patients without proper directions for administration or warnings about adverse effects and potential adverse reactions. Distribution of free samples to patients bypasses the pharmacist and thus skips a crucial safety checkpoint.

In addition, samples' child-safety packaging and instructions[6] often are inadequate for children. When studying the labels of 35 high-use drug samples, Dill and Generali[6] found that 54% lacked child-resistant packaging or warnings that the packaging was not child-resistant, 40% lacked the instruction "Keep out of reach of children," and 91% lacked the instruction "In case of accidental overdose, seek professional assistance or contact a poison control center immediately."

Our study has several limitations. We were unable to determine the extent to which drug samples are made available to safety net institutions on a national scale. If hospitals serving low-income patients prohibit the distribution of samples, then this could account for some of the disparities we report.

It is possible that some medications reported as free samples actually were free drugs provided by community clinics. On the whole, however, we think that the total number of free samples we report here is more likely to be an underestimate. Parents responding to the survey on behalf of adolescents might have been unaware of some free samples the adolescents received, particularly contraceptives or treatments for sexually transmitted diseases. Respondents might have forgotten to report samples that were received for a short time earlier in the interview reference period, although the relatively short duration of the interview reference periods (2–6 months) should minimize this recall bias. Poor or uninsured respondents might have perceived receipt of free samples as shameful or embarrassing and underreported these events; it is not our experience, however, that free samples carry such a stigma. Free samples obtained through mail order directly from manufacturers might have been undercounted but, as of 2002, the majority of such programs required that applications be filled out by a physician and that (in ~83% of cases) samples be delivered to the doctor's office.[24] Therefore, we think that most such free medications would be classified as free samples in the MEPS data. Free samples that were followed by filled prescriptions within a single interview reference period might have been undercounted. We do not have information on the total number of pills received as samples; therefore, we are unable to determine the proportion of total medications represented by free samples. Such information would be useful to obtain in future studies.

CONCLUSIONS

Our study demonstrates that poor and uninsured children are not the main recipients of free drug samples. Free samples go primarily to children with the best access to health care; their distribution does not equalize medication access. In addition, significant safety concerns are associated with the use of free drug samples. Giving free samples to children in nonurgent situations is an unproven medical practice that should be undertaken cautiously, if at all.

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Abbreviations

MEPS, Medical Expenditure Panel Survey; OR, odds ratio; CI, confidence interval; NHIS, National Health Interview Survey.

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TABLE 1

Proportions of Children Receiving ≥1 Free Sample in 2004, According to Demographic Group

	Demographic Group as Proportion of Total Pediatric Population, %[a]	Proportion of Demographic Group Receiving ≥1 Free Sample, (95% CI),%
Total (*N*=10 295)	100.0	4.9 (4.3–5.4)
Insurance status (*P*=.663)		
Uninsured part or all of year	17.5	4.5 (3.4–5.7)
Insured all year	82.6	5.1 (4.5–5.8)
Income (*P*=.237)		
<200% of poverty level	39.7	3.8 (3.2–4.4)
200% to 400% of poverty level	32.3	5.4 (4.2–6.6)
≥400% of poverty level	28.0	5.9 (4.6–7.1)
Age (*P*<.001)		
0–1 y	10.2	3.5 (2.1–4.9)
2–6 y	27.3	6.8 (5.2–8.4)
7–12 y	33.1	3.8 (3.0–4.6)
13–17 y	29.5	4.8 (3.8–5.8)
Gender (*P*=.956)		
Male	51.0	4.9 (4.1–5.8)
Female	49.0	4.9 (4.1–5.6)
Race/ethnicity (*P*<.001)		
White, non-Hispanic	58.6	6.2 (5.4–7.1)
Hispanic, any race	19.6	2.4 (1.8–3.1)
Nonwhite, non-Hispanic	21.8	3.5 (2.6–4.4)
Language (*P*<.001)		
Non—English-speaking	14.3	1.3 (0.7–1.8)
English-speaking	85.7	5.6 (4.9–6.2)
No. of medical/dental provider visits in 2004 (*P*<.001)		
0	16.4	0.7 (0.3–1.1)
1	16.3	1.8 (0.8–2.8)
2	16.2	3.5 (2.2–4.7)
≥3	51.1	7.7 (6.8–8.6)
Site of primary medical care (*P*=.022)		
No usual provider	8.8	2.1 (0.9–3.2)
Hospital (clinic or emergency department)	14.1	2.8 (1.6–3.9)
Office	77.1	5.7 (5.0–6.4)
No. of medications in 2004 (*P*=.006)		
0	51.3	
1	15.8	5.2 (3.8–6.6)
2	9.8	8.5 (5.9–11.1)

	Demographic Group as Proportion of Total Pediatric Population, %[a]	Proportion of Demographic Group Receiving ≥1 Free Sample, (95% CI),%
3–5	11.6	12.3 (9.7–14.9)
>5	11.5	15.8 (13.1–18.5)

[a] Weighted percentages are representative of the noninstitutionalized US civilian population. Totals may not add to 100 because of rounding.

TABLE 2

Multivariate Odds of Free Sample Receipt by Children in 2004

	OR (95% CI)	
	Principal Model: Controlling for Socioeconomic Factors	**Exploratory Model: Controlling for Socioeconomic Factors, No. of Medical Visits, Usual Site of Care, and Total No. of Prescription Drugs**
Insurance status		
Insured all of 2004	1 (reference)	1 (reference)
Uninsured part or all of 2004	1.05 (0.78–1.42)	1.49 (1.08–2.05)
Income		
≥400% of poverty level	1 (reference)	1 (reference)
200% to 400% of poverty level	1.00 (0.71–1.39)	1.11 (0.79–1.56)
<200% of poverty level	0.78 (0.56–1.08)	0.90 (0.63–1.29)
Age		
0–1 y	1 (reference)	1 (reference)
2–6 y	1.57 (0.86–2.85)	2.06 (1.12–3.78)
7–12 y	0.83 (0.48–1.46)	1.05 (0.59–1.85)
13–17 y	1.04 (0.61–1.77)	1.28 (0.72–2.26)
Gender		
Male	1 (reference)	1 (reference)
Female	1.00 (0.77–1.30)	1.03 (0.80–1.34)
Race/ethnicity		
White, non-Hispanic	1 (reference)	1 (reference)
Hispanic, any race	0.38 (0.28–0.52)	0.51 (0.37–0.70)
Nonwhite, non-Hispanic	0.55 (0.39–0.77)	0.72 (0.51–1.01)
No. of medical/dental provider visits in 2004		
0	NA	0.40 (0.17–0.93)
1	NA	1 (reference)
2	NA	1.77 (0.94–3.33)
≥3	NA	3.25 (1.84–5.74)
Site of primary medical care		
No usual site of care	NA	1 (reference)
Hospital-based site	NA	0.78 (0.37–1.63)
Office-based site	NA	1.52 (0.79–2.90)
Total no. of prescription medications in 2004 with refills[a]	NA	1.06 (1.05–1.08)

NA indicates not applicable.

[a] OR for incremental increase of 1 drug.

TABLE 3

Top 15 Drug Samples Distributed to US Children in 2004

Medication	Weighted No. of US Children Receiving Sample	Age, Median (Interquartile Range), y
1. Zyrtec (cetirizine; Pfizer, New York, NY)	382 774	7 (5–11.5)
2. Singulair (montelukast; Merck & Co, Whitehouse Station, NJ)	303 171	5 (4–8)
3. Zithromax (azithromycin; Pfizer, New York, NY)	240 223	8 (3–14)
4. Strattera (atomoxetine; Ely Lilly & Co, Indianapolis, IN)	226 055	12 (11–16)
5. Albuterol (Merck & Co, Whitehouse Station, NJ)	152 566	7 (5–10)
6. Elidel (pimecrolimus; Basel, Switzerland)	137 618	5 (1–7.5)
7. Rhinocort Aqua (budesonide nasal; Astrozeneca, London, United Kingdom)	131 961	8 (6–11)
8. Flonase (fluticasone nasal; Glaxo Smith Kline, Brentford, United Kingdom)	120 909	9 (8–13)
9. Amoxicillin (generic)	111 116	5 (4–7.5)
10. Augmentin/Augmentin ES (amoxicillin/clavulanate and its extended-release form; Glaxo Smith Kline, Brentford, United Kingdom)	109 253	4 (2–6)
11. Omnicef (cefdinir; Medicis, Scottsdale, AZ)	100 452	7 (5–13)
12. Nasonex (mometasone nasal; Schering, Kenilworth, NJ)	99 178	6.5 (6–11)
13. Advair Diskus (fluticasone/salmeterol inhaled; Glaxo Smith Kline, Brentford, United Kingdom)	77 997	10.5 (8–15)
14. Allegra (fexofenadine; Paris, France)	77 467	13.5 (9–15)
15. Adderall/Adderall XR (amphetamine/dextroamphetamine and its extended-release form; Shire, Hampshire, United Kingdom)	62 483	12 (11–13)

TABLE 4

Safety Concerns Regarding Pediatric Free Samples Distributed in the United States in 2004

Medication Name and Use	Weighted No. of US Children Receiving Sample	Warning	Safety Concerns
Strattera (atomoxetine), psychostimulant	226 055	Black box warning added in 2005[a]	Suicidal ideation in children and adolescents. Strattera increased the risk of suicidal ideation in short-term studies with children or adolescents with attention-deficit/hyperactivity disorder. Patients who start therapy should be monitored closely for suicidality (suicidal thinking and behavior), clinical worsening, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Strattera is approved for use for attention-deficit/hyperactivity disorder in pediatric and adult patients but not major depressive disorder Also, a medication guide is to be distributed with each prescription
Elidel (pimecrolimus), topical immunosuppressant	137 618	Black box warning added in 2006[a]	Long-term safety of topical calcineurin inhibitors has not been established. Although a causal relationship has not been established, rare cases of malignancy (eg, skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors, including Elidel cream. Continuous long-term use of topical calcineurin inhibitors, including Elidel, in any age group should be avoided, and application should be limited to areas of involvement with atopic dermatitis. Elidel cream is not indicated for use in children <2 y of age Also, a recommendation for use as a second-line treatment was added to the indications section. A medication guide is to be distributed with each prescription
Advair Diskus (fluticasone/salmeterol inhaled), inhaled steroid and long-acting β-receptor agonist	77 997	Black box warning as of 2004	Small but significant increase in asthma-related deaths in patients receiving salmeterol vs placebo. Risk may be greater for black patients, compared with white patients[b]
		Revisions to black box warning added in 2006[a]	Long-acting β_2-adrenergic receptor agonists such as salmeterol may increase the risk of asthma-related death. When treating patients with asthma, physicians should prescribe Advair Diskus only for patients who do not have adequate control with other asthma-controller medications or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies
Adderall/Adderall XR (amphetamine/dextroamphetamine and its extended-release form), stimulant	62 483	Black box warning as of 2004	Amphetamines have a high potential for abuse. Administration for prolonged periods may lead to drug dependence. There is a possibility of subjects obtaining amphetamines for nontherapeutic use or distribution to others. The drugs should be prescribed or dispensed sparingly
		Revision to black box warning added in 2005[a]	Misuse of amphetamine may cause sudden death and serious cardiovascular adverse events
		Schedule II controlled substance	
Lexapro (escitalopram; Forest, New York, NY) antidepressant[c]	46 601	Black box warning added in 2005[a]	Not approved for use in pediatric patients. Suicidality in children and adolescents. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies with children and adolescents with major depressive disorder and other

Medication Name and Use	Weighted No. of US Children Receiving Sample	Warning	Safety Concerns
Paxil/Paxil CR (paroxetine and its continuous-release form; Glaxo Smith Kline, Brentford, United Kingdom), antidepressant[c]	21 695		psychiatric disorders. Patients who start therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber
Ritalin (methylphenidate; Basel, Switzerland), stimulant[c]	5689	Black box warning before 2004	Drug dependence. Ritalin should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism; such patients may increase dosage on their own initiative. Chronically abusive use can lead to marked tolerance and psychic dependence, with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal; severe depression and chronic overactivity can be unmasked
		Warning added in 2006 (not black box)	Serious cardiovascular events. Sudden death was reported in association with central nervous system stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems
		Schedule II controlled substance	

Data were obtained from the *Physicians' Desk Reference* and the Food and Drug Administration Web site (www.fda.gov). Information on black box warnings was taken from medication labels.

[a] Dates refer to the date the Food and Drug Administration approved the black box warning or revision. These warnings typically appear in the *Physicians' Desk Reference* the following year.

[b] Beginning in 2006, the possible risk difference for black patients was no longer emphasized in the black box warning but was discussed in the warning section.

[c] Not among the top 15 samples given to children.