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Predictors of Polypharmacy and Off-Label Prescribing of Psychotropic Medications: A National Survey of Child and Adolescent Psychiatrists

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Abstract

We employed a national survey of child psychiatrists to examine typical prescribing practices for children with anxiety, depression, and disruptive behavior disorders. We examined the extent to which polypharmacy and off-label prescribing occur in routine practice and the degree to which child characteristics, child psychiatrist characteristics, and medication availability may influence these prescribing practices. We found that child psychiatrists most often prescribed medications that were on-label according to U.S. Food and Drug Administration (FDA) guidelines, and that they were progressively less likely to choose medications with partial approval (i.e., medications having pediatric approval but not for the patient's age or problem type), and then medications with no pediatric approval. We also found that prescribing multiple concomitant medications was the norm. We employed best subsets regression to determine the best theoretically relevant predictors to explain polypharmacy and off-label prescribing and found that the best fitting model only included number of child diagnoses. These findings suggest that comorbidity is an important issue in the pharmacotherapy of children with mental health disorders and one that must be addressed in future clinical trials. (*Journal of Psychiatric Practice* 2014;20:438–447)

Keywords

prescribing practices; polypharmacy; off-label prescribing; pediatric psychopharmacology; comorbidity

Researchers have expressed concerns about widespread off-label prescribing (i.e., the prescription of medications without U.S. Food and Drug Administration [FDA] approval for the condition or population to whom they are being prescribed) and polypharmacy (i.e., the concurrent prescription of multiple psychotropic medications) with youths because of the limited evidence on the efficacy and safety involved in both practices.[1,2] Both practices have been widely reported in child and adolescent psychiatry and in the larger field of pediatrics,[3–8] with some estimates as high as 80% of prescribed medications being off-label[6] and estimates of polypharmacy being 52.4%.[9] While polypharmacy and off-label use of

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medication may at times involve prescribing based on a more limited evidence base, they are not necessarily based on no evidence.[10] In some patients, they may be cutting-edge, research-supported, or standard practices that are simply ahead of FDA approval.[7,11] In many patients, however, they lack solid scientific evidence[12] and can thus be risky.

More specifically, off-label prescriptions may lack evidence of safety or efficacy. Prescribing that is offlabel for age may be risky due to developmental influences on the absorption, distribution, metabolism, excretion, or toxicity of medications[13] and the risk for side effects[14,15] in children. Prescribing that is off label for problem type may pose concerns about efficacy.[12,16] When improperly treated, early onset psychiatric disorders are linked to negative long-term outcomes.[17,18] Similarly, polypharmacy can also be unsafe due to the increased risk of side effects.[19] It can also raise concerns about efficacy if the effect of one medication interferes with that of another, or if the prescription entails a complicated medication regimen that reduces patient adherence.[20]

Previous surveys and chart reviews have examined predictors of polypharmacy,[1] off-label prescription of second-generation antipsychotic medications (SGAs),[21,22] and prescribing of psychotropic medica-tions to preschoolers.[23] These studies suggest that several patient, medication, and physician characteristics may influence polypharmacy and off-label prescribing. These characteristics include patient demographics, such as the age of the child (being older),[24–26] sex (being male),[24,27] race (being white),[28] diagnosis (having an externalizing disorder),[21] comorbid diagnoses,[26,29–31] and greater severity of problems.[30,32,33] Child psychiatrists' personal characteristics, knowledge, attitudes, and work-related behaviors, such as reading professional journals,[34,35] discussions with colleagues,[30,31] continuing medical education,[31] and receiving in-service training[31] may also be important predictors of prescribing decisions. In contrast, the psychiatrist's age, years of experience, overall patient volume, board certification, conference attendance, and medical school affiliation have not been shown to predict prescribing.[35] Finally, the availability of FDA-approved medications for pediatric use may be important; only 20%–30% of FDA-approved medications have approval for pediatric use.[36] Therefore, there are likely many child cases for which no on-label medication options exist.

The goals of this study were to evaluate the frequency of off-label prescribing and of polypharmacy in a sample of practicing child and adolescent psychiatrists and identify the case characteristics, psychiatrist characteristics and/or medication characteristics most strongly predictive of these two practices. This information may help identify gaps in available treatment resources, identify common medication practices, and suggest areas for future research.

METHODS

As part of a large mail survey of 5,000 mental health providers conducted from fall 2007 to spring 2008,[37–39] 1000 psychiatrists were randomly selected from the population of 5,341 active members of the American Academy of Child and Adolescent Psychiatry (AACAP). Each was mailed a 5 page questionnaire, designed using the Tailored Design Method, a survey design methodology shown to maximize response rate.[40] The survey covered

psychiatrists' demographics, training and education, work activities, work setting, caseload, and usual assessment and treatment strategies. The questions developed for the survey were pilot tested with two samples of mental health providers (n = 500 in a pilot mailed survey; n = 14 in a series of focus groups) prior to being used in this study.[37–39] Each psychiatrist was randomly assigned to receive one of three versions of the survey that asked about the strategies used with a recent, representative child case treated for a primary presenting problem of 1) anxiety, 2) depression, or 3) disruptive behavior. Clinicians were also asked to provide the age, sex, primary diagnosis, and secondary diagnoses of this recent case and asked whether the child received psychotherapy and/or psychotropic medication. For all children receiving medication, the psychiatrist was also asked to list all psychotropic medications prescribed. Psychiatrists responded by checking the appropriate boxes for child age and sex, and checked yes or no for a) whether the child received psychotherapy and b) whether the child received medication. They provided the names of diagnoses and psychotropic medications using a free response format. All procedures were approved by the relevant institutional review board.

Participants

Of the 1,000 psychiatrists mailed a survey, 81 had undeliverable addresses. Of the 919 psychiatrists who were presumably reached via mail, 408 (44.4%) responded to the survey, a rate comparable to the 24%–49% response rates seen in previous surveys of child psychiatrists.[35,41] Of the respondents, 103 (11.2%) did not provide direct service to youths and their responses are not used in this report. Of the 305 (33.2%) psychiatrists currently working with youth, 226 (24.6%) provided sufficient information about the medication(s) prescribed to a recent, representative case to permit coding and inclusion in the final sample. Based on a review of other published surveys done with child and adolescent psychiatrists, [41–45] we expected that our sample of psychiatrists would be approximately 53% male, 74% Caucasian, 13% Asian American, 6% Hispanic, 4.7% Asian American, and 3% other. We also expected that our sample of psychiatrists would be on average 47 years of age, have about 11 years of experience, work approximately 43 hours per week. We expected approximately 41% would work in private practice, 48% in outpatient clinics, 4% in a university setting, and 7% in an inpatient setting. Examination of Tables 1 and 2 indicates that our sample had somewhat more years of experience and were more likely to work in inpatient settings, outpatient settings, and university settings than child and adolescent psychiatrists who had participated in previous published surveys.

Measures

Polypharmacy was determined by summing the number of different medications psychiatrists listed in their description of a recent representative case. Polypharmacy was used as one of the dependent variables.

Off-label medication risk.—We first consulted a standard psychopharmacological textbook[46] and the medical database Epocrates Online©,[47] to generate a comprehensive list of psychotropic medications available in the United States. We then found the corresponding FDA labels in the 2007 Physician's Desk Reference,[48] the Physician's Desk Reference Online©,[49] the FDA's official website,[50] and on http://dailymed.nlm.nih.gov/dailymed/

about.cfm, the website suggested by the FDA (FDA, Division of Drug Information, Center for Drug Evaluation and Research, personal communication, October 28, 2010). For each medication, we recorded in a chart the approved indication and age from the information listed in the label section "Indications and Usage" (see Appendix 1).

Using a coding manual (available from the authors upon request), two undergraduate research assistants and the first author coded each medication to capture the risk inherent in each prescription choice as 1 = on-label to convey a lower, but not zero risk, given potential side effects, 2 = partial approval (having pediatric approval but used off-label for either age or problem type) to convey medium risk, or 3 = no pediatric approval (used off-label for both age and problem type) to convey the greatest risk. Medications were coded "on-label" for any disorder within a category for which the particular medication is approved. For example, a medication approved for schizophrenia would also be considered "on-label" if the disorder listed was psychotic disorder not otherwise specified (NOS). We made a distinction, however, for disorders that the FDA considers separately in its labeling such as obsessive-compulsive disorder (OCD) and anxiety. For example, at the time of the study, the label for sertraline specified that it had an indication for OCD in both children and adults, but that it was indicated only in adults for social anxiety disorder, major depressive disorder, premenstrual dysphoric disorder, and posttraumatic stress disorder.

A random sample of 20% of responses was selected to assess interrater reliability, with kappas found to range between 0.90 and 0.97 ($p < 0.001$).

A summary variable, Total Risk, captured both the cumulative risk involved in prescribing off-label medications and the use of multiple medications. For example, if a respondent described using three medications: the first on-label (1), the second with partial approval (2), and the third with no pediatric approval (3), the Total Risk for this medication regimen was computed as 1 + 2 + 3 = 6.

To examine the impact of changes in approval status and thus whether research supporting practices may have outpaced FDA's formal approval, the coding process was completed twice: once according to the FDA drug labels approved on or before June 2008 (the time of the data collection) and another with the labels approved on or before December 2010 (the time of data analysis). The average medication risk based on the 2007 FDA approvals was mean Total Risk = 2.734 (SD = 1.918). The average medication risk based on the 2010 FDA approvals was mean Total Risk = 2.473 (SD = 1.713). The Total Risk variables for each of these time periods were examined separately as dependent variables.

Statistical Analyses—We examined 13 possible explanatory variables, selected based on the available empirical and theoretical literature. With regard to the patient, we examined the child's sex, the child's age, presence of a disruptive behavior disorder, a sex by behavior disorder interaction term, and the patient's total number of diagnoses. With regard to the psychiatrist, we examined board certification, size of caseload, years since completion of training, percentage of training specific to children and adolescents, positive attitude toward empirically supported practices, frequency of reading scientific journals, and frequency of talking to colleagues about new practices. For the last three items, psychiatrists were asked

to use a 5-point Likert-type scale ranging from 1 = strongly disagree to 5 = strongly agree to rate the extent to which they agreed with each of the following statements: "I like to try new types of practices that have been supported by research," "I regularly read professional journals or books relevant to my work," and "I regularly talk to colleagues about new practices relevant to my work." We also examined medication availability, the number of FDA-approved medications available for a child of a given age and problem type in 2007 and 2010 (note that we treated medications that come in a variety of formulations, such as extended release and chewable vs. tablet, as a single medication). To calculate medication availability, we counted how many medications had FDA approval in 2007 and 2010 for each representative treatment case based on age and specific disorders. In order to identify predictors of off-label prescribing, we then conducted best subset regression analyses using the medication risk variable as the dependent variable. The best subset regression procedure identifies models containing the best subset of predictors according to Mallow's C_p criterion.[51] See Table 1 for descriptive statistics of these variables.

RESULTS

Please see Table 2 for provider characteristics, Table 3 for characteristics of the recent case, and Table 4 for the top medications prescribed.

Polypharmacy: Frequency and Predictors

In their treatment of a recent representative case, 60.6% of psychiatrists reported prescribing only one medication, 29.6% prescribed two medications, and 9.7% prescribed three or more medications (mean = 1.52 medications, SD = 0.75, range= 1–5). Using best subset regression analyses with the Mallow's C_p criterion, we identified five models containing the best subset of predictors for total number of medications prescribed. Across these models, and with both 2007 and 2010 standards, the total number of child diagnoses was the most consistent predictor, appearing in all 5 models. Thus, in our final model, only total number of diagnoses remained. Total number of child diagnoses significantly predicted total number of medications and accounted for 13% of the variance in polypharmacy ($F[1, 225] = 34.79$, $p < 0.001$, $B_1 = 0.205$, $p < .001$, [95% CL 0.137–0.274], $\beta = 0.370$].

Off-Label Prescribing: Frequency and Predictors

Using the 2007 FDA approvals, 44.9% of all psychotropic medications were prescribed completely on-label and 30% were prescribed partially off-label, with 0.06% of the medications not having approval for a patient of that age and 29.44% not having approval for the problem type. The results for age and problem type were combined into a single category because of the low frequency of off-label use for age only. Finally, 25.1% were prescribed with no pediatric approval. When examined using the 2010 standards, 50.9% of all psychotropic medications were prescribed completely on-label, 34.8% were prescribed partially off-label (0.6% for age and 34.2% for problem type), and 14.3% were prescribed with no pediatric approval, reflecting updates in labeling that occurred between the two time periods.

In order to identify predictors of off-label prescribing, we then conducted best subset regression analyses, first using the 2007 medication risk variable as the dependent variable, and then using the 2010 medication risk variable as the dependent variable. In both instances, we identified five models containing the best subset of predictors according to Mallow's C_p criterion and found again that total number of child diagnoses was the most consistent predictor, appearing in all 5 models. Total number of child diagnoses was also the only significant independent variable predicting total risk in both the 2007 and 2010 periods. In the final model for 2007, only total number of diagnoses significantly predicted total risk; it accounted for 5.25% of variance in off-label prescribing ($F[1, 225] = 13.47$, $p < 0.001$, $B = 0.341$, $p < 0.001$ [95% CL 0.158–0.524], $\beta = 0.238$).

Our final model for 2010 also contained only total number of diagnoses as a predictor for total risk; it accounted for 4% of the total variance ($F [1, 225] = 10.31$, $p < 0.001$, $B= 0.268$, $p = 0.002$ [95% CL 0.104–0.433], $\beta = 0.21$).

DISCUSSION

Using a national survey of child psychiatrist members of the AACAP, we examined prescribing practices for children with anxiety, depression, and disruptive behavior disorders. We examined the frequency with which respondents prescribed multiple concurrent psychotropic medications (polypharmacy) and the frequency with which they prescribed medications on-label, partially off-label, and with no pediatric approval. We also looked at the degree to which case characteristics, psychiatrist characteristics, and medication availability influenced polypharmacy and off-label prescribing practices.

Consistent with past research,[1,3–6] we found high rates of polypharmacy and off-label prescribing. Specifically, 39.4% of recent child cases were prescribed more than one psychotropic medication and 55.1% of the psychotropic medications prescribed were partially or fully off-label. However, when we examined these frequencies using our conceptualization of risk, we found that, consistent with expectations, the largest percentage of medications were being prescribed on-label (44.9%), with progressively fewer medications prescribed with partial approval (30%) and with no pediatric approval (25.1%).

This rank ordering did not change across the 2007 and 2010 periods. Between the two periods, however, decreases in the percentages of off-label prescriptions reflected changes in approval status. For example, the top two medications without pediatric approval during the 2007 period, escitalopram oxalate and quetiapine (Table 4), had gained pediatric approval by 2010, suggesting that several respondents may have been aware of pending FDA approval or of the clinical trial findings that supported subsequent approval, when they prescribed those agents. Interestingly, we did not find that more positive attitudes toward empirical evidence, reading journal articles, or talking to colleagues significantly influenced prescribing practices in either period. It may be that respondents were aware of the findings through other means (e.g., information from pharmaceutical companies or thought leaders in the field[52]) or that some other variable not included in the survey influenced their decision.

Of course, many instances of off-label prescribing remained even after accounting for up to a 3-year delay in official FDA approval. It is worth noting that ambiguity in FDA labels may also contribute to off-label prescribing. As one example, we found the 2007 label for clonidine, the third most prescribed medication without pediatric approval (Table 4), was ambiguous as to whether or not it had pediatric approval. This ambiguity led the FDA to require a label change in 2009 for clonidine that clarified that it was not approved for pediatric use (FDA personal communication, October, 2010).

Strikingly, although we examined 13 potential predictors, the single best fitting model for both polypharmacy and off-label prescribing across the two periods included just one predictor: total number of child diagnoses. None of the other child characteristics (sex, age, the presence of an externalizing disorder, or a sex by externalizing interaction), psychiatrist characteristics (caseload, board certification, experience, % of child specific training, use of journal articles, talking to colleagues, or attitudes toward scientific evidence), or even the number of FDA approved medications available for the child's age and presenting problem(s) was a significant independent predictor beyond number of child diagnoses.

Strengths and Limitations

Overall, this study had several strengths, including the extension of the existing literature by examining polypharmacy and off-label prescribing practices, the introduction of a novel conceptualization of the off-label prescribing decision, and the production of a comprehensive chart listing psychotropic medications with pediatric approval.

Nevertheless, this study was not without limitations. First, despite having a response rate (44.3%) comparable to the higher end of those found in previous surveys of psychiatrists,[35,41] missing data resulted in a smaller number (n = 226) of cases available for analysis. Furthermore, missing data on specific variables (e.g., 100 responders skipped the item asking about board certification) prevented us from examining the impact of some potentially important variables on prescribing practices. Second, the coding scheme used for both off-label prescribing and polypharmacy may not have fully captured the complexity of information important to the decision-making process and/or the level of risk associated with the practice. Third, FDA approval is not necessarily a gold standard.[7,11,53] Some approved medications may have higher incidents of side effects than unapproved medications or may only be beneficial in the short run.[54–56] In addition, other medications that have been empirically demonstrated to be safe and efficacious for a specific use may lack FDA approval for that use,[57,58] perhaps because the data have not been submitted to FDA review due to a lack of financial incentives.[7] Despite these limitations, we used FDA approval as our benchmark because a) it requires scientifically rigorous safety and efficacy data, b) it is the standard used by researchers expressing concerns about off-label prescribing, and c) the FDA is currently the highest regulatory body for medications in the United States. Several variables relevant to evidence-based psychiatric practice were not addressed by the survey (e.g., dosage and titration, previous treatments attempted, and medication allergies) and may further explain prescribing practices. Third, the sample was restricted to members of the AACAP; as such, the findings may not generalize to the many general practitioners who are increasingly providing the majority of psychotropic prescriptions to children.[59] Academy

members, by virtue of their advanced training and continued professional involvement, may well be those most likely to a) remain abreast of clinical trials research, b) be referred and thus treat the most complex cases, and thus c) potentially have higher rates of off-label prescribing and polypharmacy than would be seen among a more generalist physician sample. Fourth, there are many well-documented limitations in using self-reports (e.g., response bias, self-selection bias). Fifth, the high levels of comorbidity in the cases described (90.3% of cases had more than one significant psychiatric problem type) prevented us from being able to run separate analyses for each diagnostic category. Related to this, we did not have information about other characteristics of the patients, such as race or ethnicity, diagnostic chronicity, or whether they were medication naïve or had already failed other medication trials, factors that may well have influenced prescribing practices.

CONCLUSIONS

Comorbidity as the single significant predictor of both polypharmacy and off-label prescribing in youth highlights a critically important gap between research and practice in child psychiatry. In our study, as in others,[60] comorbidity was the rule rather than the exception. As such, simply treating each distinct disorder with a separate medication will result in polypharmacy for most of the children seen in routine psychiatric practice. Each additional medication prescribed may also result in a greater likelihood that at least one of those medications will be off-label. Furthermore, because comorbidity is often associated with greater symptom severity,[18] cases with comorbidity may be more difficult to treat and may not experience adequate improvement when treated with a single available on-label medication.

In order to provide the highest quality care to children, healthcare providers must have empirical information about optimal treatment practices for children with comorbid disorders. However, most clinical trials are conducted on a single medication targeting a single diagnosis in children.[61] While a handful of clinical trials have addressed issues of comorbidity[62,63] or the use of polypharmacy,[64-66]overall, available evidence on how to treat children with more complex case presentations is lacking. The findings from our study suggest that more clinical trials focused on medication combinations and treatment of common co-occurring conditions are needed.

Appendix

Appendix 1.

Appendix 1. Psychotropic medications with pediatric approval according to the 2007–2010 FDA drug labels

Generic name	Trade name	Approved indication	Age	Generic name	Trade name	Approved indication	Age
Amphetamines, mixed salts	Adderall	ADHD	6+	Imipramine	Tofranil	Enuresis	6+
				Lisdexamfetamine	Vyvanse	ADHD	6+
Aripiprazole	Abilify	Autism*	6+				
		(irritability)		Methamphetamine	Desoxyn	ADHD	12+
		Bipolar	10+	Methylphenidate	Concerta	ADHD	6+
		(mania)			Daytrana	ADHD	6+
		Schizophrenia	13+		Methylin	ADHD	6+
					Ritalin	ADHD	6+
Atomoxetine	Strattera	ADHD	6+				
Chlorpromazine	Thorazine	Behavioral problems	12-Jan	Methylphenidate HCl	Metadate CD	ADHD	6+
Clomipramine	Anafranil	OCD	10+	Olanzapine	Zyprexa	Bipolar (mania)*	13+
Desmopressin acetate	Desmopressin acetate	Enuresis	6+			Schizophrenia*	13+
				Pimozide	Orap	Tourette's syndrome	12+
Dexmethylphenidate	Focalin	ADHD	6+				
Dextroamphetamine	Dextrostat	ADHD	6+	Quetiapine	Seroquel	Bipolar* (mania)	10+
Dextroamphetamine sulphate	Dexedrine	ADHD	6+			Schizophrenia*	13+
				Risperidone	Risperdal	Autism (irritability)	5+
Escitalopram	Lexapro	MDD*	12+				
Fluoxetine	Prozac	MDD	7+			Bipolar (mania)	10+
		OCD	8+			Schizophrenia	13+
Fluvoxamine	Luvox	OCD	8+				
				Sertraline	Zoloft	OCD	6+
Guanfacine	Intuniv	ADHD*	6+				
Haloperidol	Haldol	Behavioral problems	12-Mar				
		Hyperactivity	12-Mar				
		Tourette's syndrome	12-Mar				

*Medication received FDA approval for this indication after July 2008.

ADHD: attention-deficit/hyperactivity disorder

MDD: major depressive disorder syndrome

OCD: obsessive-compulsive disorder

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Table 1.

Variables used in the analysis

Child characteristics	
% Male	66.2 %
Age	
3–6 years old	2.8%
7–10 years old	35.9%
11–13 years old	18.9%
14–17 years old	42.4%
Presence of a behavior disorder	53.5%
Total number of diagnoses mean (SD)	3.05 (1.34)
Medication availability *	
2007 mean (SD)	8.65 (6.76) meds
2010 mean (SD)	9.22 (7.32) meds
Psychiatrist characteristics	
Caseload, mean (SD)	152 active cases (176)
Board certification (n = 126)	65.1%
Years of experience mean (SD)	21.6 years (11.1)
% who had received child specific training mean (SD)	60.13% (20.38)
Positive attitude toward empirically based practices mean † (SD)	4.18 (0.68)
Regularly read journal articles mean † (SD)	4.11 (0.78)
Regularly talk to colleagues mean † (SD)	3.93 (0.88)

SD: standard deviation

*Calculated based on the number of medications with FDA approval for each representative treatment case based on age and specific disorders; thus, there were a mean of 8.65 FDA-approved medications per patient in 2007 and 9.22 in 2010.

†Rated on a scale ranging from 1 = strongly disagree to 5 = strongly agree

Table 2.

Provider characteristics

Demographic characteristics	
% male	55.6 %
Age, mean (SD) in years	50.28 years (11.095)
Ethnicity	
White/Caucasian (non-Hispanic)	77.8%
Hispanic/Latino	5.3%
Black/African American	3.1%
Asian/Pacific Islander	12.0%
Mixed/Other	2.2%
Work setting	
Elementary, middle, or high school	2.7%
Higher education setting	20.9%
Outpatient clinic	33.8%
Private practice	42.2%
Day treatment facility	4.4%
Residential facility or group home	8.4%
Inpatient hospital or medical clinic	19.6%
Managed care organization	1.8%
Other	11.6%
Professional characteristics	
Hours worked per week mean (SD)	43.23 hours (14.36)

SD: standard deviation

Table 3.

Characteristics of the recent representative case

Total number of diagnoses mean (SD)	3.04 (1.339)
Anxiety	64.6%
Depression	58.4%
Disruptive behavior disorders	53.5%
Autism	2.7%
Learning disorder	20.8%
Eating disorder	2.2%
History of abuse/trauma	24.8%
ADHD	48.7%
Tourette's syndrome	0.4%
Bipolar disorder	2.7%
Enuresis	0.4%
OCD	10.6%
Intellectual disability	4.9%
Substance abuse	9.3%
Schizophrenia	0.4%

ADHD: attention-deficit/hyperactivity disorder

OCD: obsessive-compulsive disorder

SD: standard deviation

Table 4.

Medications used in overall patient sample (using 2007 standards)

Total number received, mean (SD)	1.52 medications (0.75)
Top 3	
	Sertraline (15.5%)
	Fluoxetine (14.9%)
	Methylphenidate (8.5%)
Top 3 on-label	
	Fluoxetine (26%)
	Methylphenidate (18.8%)
	Amphetamine mixed salts (11.7%)
Top 3 partially off-label	
	Sertraline (39.8%)
	Risperidone (13.6%) Fluoxetine (10.7%)
Top 3 no pediatric approval	
	Escitalopram oxalate (19.8%)
	Quetiapine (18.6%) Clonidine (11.6%)

SD: standard deviation