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Side Effects from Use of One or More Psychiatric Medications in a Population-Based Sample of Children and Adolescents

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Abstract

Objective: The purpose of this study was to investigate the side effect risks from using one or more psychiatric medications (including antipsychotics, antidepressants, α-2 agonists, benzodiazepines, mood stabilizers, and stimulants) among a national cohort of children and adolescents.

Methods: A questionnaire survey was administered to parents who filled a prescription for a psychiatric medication for their child at a large national retail pharmacy chain. Primary outcome variables were the total count of side effects from a list of 12 problem areas, as well as parent-reported side effect intensity (mild/moderate/severe). Modifiers investigated included specific medication and number of medications utilized, demographics, and difficulties with access to care.

Results: A total of 1347 parents of study subjects ages 3–17 years from 30 U.S. states who were taking psychiatric medications for any indication purchased at one retail pharmacy chain enrolled following a single mail invitation (7.5% response). Of the study subjects, 80% were white/non-Hispanic, 64% were male, 63% had private health insurance, and 67% had used a current medication for >1year. Most (84%) had one or more parent-reported side effect. After adjusting for covariates, subjects with two medications reported 17% ($p < 0.001$) and with three or more medications reported 38% ($p = 0.002$) increases in their average number of side effects than did children taking one medication. Parental reporting of difficulties in accessing care also predicted a 42% ($p < 0.001$) greater number of side effects than for those who had no access difficulties. Side effects were particularly more common in medication combinations including either selective serotonin reuptake inhibitors (SSRIs) (77% higher odds, $p < 0.001$) or antipsychotics (99% higher odds, $p < 0.001$).

Conclusions: Side effects from psychiatric medications appear to be both more common and more severe overall with increasing numbers of medications utilized, and with perceived difficulty in accessing care. Polypharmacy regimens including either SSRIs or antipsychotics were especially associated with experiencing side effects, within this study sample.

Introduction

Pediatric psychiatric polypharmacy, defined as the receipt of multiple daily psychiatric medications for the same or for different conditions, has been increasing. In the decade leading up to 1996, there was a reported sevenfold increase in pediatric psychiatric polypharmacy, with a continued but lower rate of rise (twofold increase) reported through 2007 (Olfson et al. 2002; Zonfrillo et al. 2005; Comer et al. 2010). Concerns about this include a lack of research evidence supporting the effectiveness of most medication combinations, poorly defined side effects from medication combinations, and increased costs that may or may not be supported by increased benefits for patients (NASMHPD 2001; McClellan and Werry 2003; AACAP 2009). For the few combinations that have been researched for clinical effectiveness in children (e.g., stimulant plus α-2 agonist), long-term outcomes and side effects remain unreported. Despite previous calls for gathering better data, there continue to be few data-driven recommendations available to inform the use of psychiatric polypharmacy among children (Jensen et al. 1999; Breland-Noble et al. 2004; AACAP 2009).

Research on pediatric psychiatric polypharmacy is needed, but continues to be very limited, for reasons that include procedural challenges in polypharmacy trials over monotherapy trials,

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recruitment and retention difficulties for child psychopharmacology research (which leads to higher costs than with adults), and limited research funding available from industry and federal agencies (NASMHPD 2001; Hughes et al. 2006). Alternative data gathering strategies are needed to detect the real world outcomes experienced by patients (Markoff 2013).

To accomplish this goal, we adopted a novel recruitment strategy, inviting parents whose children had prescriptions filled for psychiatric medications at a large, national retail pharmacy chain to complete a survey about the medication experiences of their children. Unlike studies of prescribing patterns in specific clinical populations or based on insurance claims files, this strategy incorporates the experiences of children and youth in community-based care settings across a broad range of health insurance, geographic, and sociodemographic profiles. Our recruitment strategy was intended to efficiently obtain a large, adequately powered national cohort for pattern detection within the highly diverse population of all children and adolescents using psychiatric medications.

In this article, we examine the number of parent-perceived side effects and their severity among children and adolescents with differing levels of psychiatric medication use in a general community sample of those using medications. In a subanalysis, we investigated specific drug classes used alone and in combination, for their associations with the study outcomes.

Methods

This study is the first reported use of data collected for the Child Psychopharmacological Experiences Survey (CPES), a longitudinal survey of parents designed by the authors to study the demographic, symptom, and psychiatric treatment plan profiles of children and youth who were prescribed psychiatric medications in current community practice. A copy of the survey is available from the corresponding author on request. All parents or legal guardians with a child between ages 3 and 17 years who filled a prescription within the previous month for at least one psychiatric medication in the Kroger retail pharmacy system–a network of pharmacies with 22 individual regional brands in 31 states nationwide–were eligible to participate in the CPES. These parents received a single mailed study invitation letter describing the ~30 minute long survey, with the option of completing via the Internet or U.S. mail upon request. Unique survey activation codes were assigned, to assure that each household enrolled only one child. Survey respondents received a $10 gift card by mail to thank them for their participation. All research procedures were approved by the Seattle Children's Institutional Review Board, and funded by a grant from the HRSA Maternal Child Health Bureau.

Both the number and severity of side effects were examined. More thorough and accurate pediatric side effect reporting has been noted to come from a standardized symptom review rather than from open-ended queries about side effects (Greenhill et al. 2004). However, because we were unable to locate a brief parent rating scale that could provide this information applicable to any psychiatric medication, we created a set of side effect survey questions for parents modeled after the 10 body systems side effect interview items from the Research Units on Pediatric Psychopharmacology (RUPP) Safety Monitoring Uniform Research Form (SMURF), (Greenhill et al. 2004). These items included weight gain, weight loss, gastrointestinal upset, headaches, insomnia, irritability, fatigue, eye problems, tremors, or problems with blood tests. Two novel but clinically important side effects were added to register intentional self-harm and suicidality attributed to medication. Clinical importance of experienced side effects was further assessed by asking respondents to rate the intensity of each problem as being either mild, moderate, or severe. Prior to implementation, these side effect survey items (along with our other survey questions) were tested, and then modified to maximize validity through cognitive debriefing with 10 parents of children taking psychiatric medications, to test the wording, understandability, and order of the survey questions using standard procedures from the U.S. National Center for Health Statistics Cognitive Survey Laboratory (Jabine et al. 1984).

Baseline covariates were selected *a priori* on the basis of theoretical relevance, and were grouped as demographics, duration of prescription drug use, access to mental healthcare, and comorbidities. Demographics included age groups representing early and late childhood, and early and late adolescence (3–9, 9.1–12, 12.1–15, 15.1–19 years), sex, and race (white/non-Hispanic vs. other). Because the length of prescription drug use could confound the effect of polypharmacy on reported side effects (e.g., well tolerated medications might be more likely to be continued), we controlled for the child's longest duration of use (≤1 year or >1 year). To account for differences in mental healthcare use, we considered whether a subject reported any difficulty in access to mental healthcare services or had an insurance type (none, public only, at least some private insurance) that may have influenced their access to care. Similarly, the number of siblings in a family (none, one, or more than one) and the family's annual income in U.S. dollars (<25,000, 25–50,000, 50–75,000, 75–100,000, 100–150,000, >150,000) were queried, as they may have related to an ability to utilize care or to focus more monitoring on the child. As access to mental healthcare could vary geographically, we controlled for region of residence in the United States (Midwest, South, and West). Characteristics of the total invited sample were provided by our pharmacy partner in an aggregate, de-identified form including age, sex, region of residence, and type of health insurance.

Our primary predictor of interest was polypharmacy captured as a categorical measure of the number of psychiatric medications (1, 2, ≥3). For secondary analysis, subjects who used a drug of a specific class were identified using an indicator variable for each of the following drug classes: antipsychotics, benzodiazepines, mood stabilizers, noradrenergic attention-deficit/hyperactivity disorder (ADHD) medications, central α agonists, stimulants, tricyclic antidepressants, serotonin-noradrenergic reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), and other antidepressants/anxiolytics. In order to avoid sparse observations in categories of polypharmacy defined by use of a drug class, we redefined polypharmacy to reflect use of more than one medication.

Statistical analysis

We used a nonparametric Kruskal–Wallis test to measure association between the number of side effects and baseline covariates, including levels of medication use. The side effects were further explored by comparing the proportion of subjects reporting severity levels by the type of side effects and the levels of medication use.

In adjusted analyses for the number of side effects and side effect severity, we controlled for observable differences between exposure groups, to isolate the independent effect of polypharmacy. A negative binomial model was fit to the number of side effects, in order to investigate differences between different levels of medication use adjusting for other baseline covariates. To facilitate the interpretation of results comparing subjects using two or more medications with those using only one medication, we present

adjusted risk ratios that estimate multiplicative increase in the average number of side effects. In a separate analysis with multiple observations per subject, a generalized multivariate binomial model was fit with independent correlation structure to assess odds of moderate or severe side effect intensity by levels of medication use and type of side effects. No adjustment was made for multiple comparisons. Reported *p* values should, therefore, be interpreted in the context of the number of separate hypothesis tests corresponding to multiple measures. The risk of type 1 error was mitigated by focusing on outcomes selected *a priori*.

In a subanalysis, we estimated the relative risk of side effects associated with a specific drug class when used with other drugs versus when used alone. For this purpose, for each drug class, we fit a negative binomial model to the number of side effects adjusted for baseline covariates and an interaction between the drug class and polypharmacy indicator (yes vs. no). The risk ratio estimates the multiplicative increase in the average number of side effects associated with a specific class drug when used with other medications compared with when used without. In particular, two drug classes were further studied for the types of side effects, and reported severity in an exploratory setting.

Results

Characteristics of the study sample

A total of 1376 families out of 18,337 receiving a single one page study invitation letter mailed directly from the Kroger pharmacy's in-house mailing system, elected to fully complete the baseline wave of the survey. Comparing respondents with the total invited sample, there were no statistically significant differences in age or sex of the child, or in the region of family residence. However, there were slightly fewer privately insured children in the respondent group relative to the total invited sample, private/commercial health insurance 62.9% versus 71.3% among those reporting their insurance status.

Of all the respondents, 1347 (98%) reported their child to be currently on psychometric medications. This sample of 1347 children constituted our study population, with a 1.2% missing response rate on side effect outcomes. Subjects who were white/non-Hispanic (80%), male (64%), using only one psychiatric medication (61%), and those with some private health insurance (63%) dominated the study population (Table 1). Most (67%) had been using at least one of their psychiatric medications for > 1 year. The three most common psychiatric medication classes included stimulants (64%), SSRIs (24%), and antipsychotics (18.5%). Parents commonly reported that their children experienced unwanted side effects from the use of psychiatric medications, with 84% of the total sample noting that their child experienced at least one side effect of any type or severity.

Unadjusted estimates of side effects

On average, the number of side effects did not vary significantly with age, gender, race, family size, or region of residence, and it varied only marginally with family size and insurance type, but varied

Table 1. Number of Side Effects (Unadjusted for Covariates)

			Number of side effects		
	Levels	n = *1347*	n	*Mean (SD)*	*Kruskal-Wallis test* p *value*
Age (in years)	age ≤ 9	312	309	2.27 (1.68)	0.275
	9 < age ≤ 12	366	363	2.52 (1.91)	
	12 < age ≤ 15	343	339	2.58 (2.01)	
	age > 15	326	320	2.71 (2.23)	
Gender	Male	861	853	2.44 (1.82)	0.413
	Female	486	478	2.67 (2.21)	
Race	Nonwhite	181	180	2.69 (2.05)	0.218
	White	1084	1083	2.48 (1.94)	
Maximum duration of any utilized medication	≤ 1 year	446	442	2.4 (2.01)	0.039
	> 1 year	900	888	2.58 (1.95)	
Care access difficulties	No	870	856	2.15 (1.73)	< 0.001
	Yes	477	475	3.19 (2.18)	
Family size	No siblings	335	335	2.71 (2.02)	0.085
	1 sibling	513	513	2.46 (1.93)	
	> 1 siblings	417	415	2.42 (1.95)	
Health insurance	None	26	26	2.5 (2.73)	0.077
	Only public	386	385	2.71 (2.08)	
	Some private	852	851	2.42 (1.88)	
Household income	< $25,000	220	220	2.78 (2.17)	< 0.001
	$25,000 to $49,999	277	276	2.91 (2.08)	
	$50,000 to $74,999	265	265	2.26 (1.89)	
	$75,000 to $99,999	198	197	2.44 (1.96)	
	$100,000 to $149,999	193	193	2.19 (1.72)	
	> $150,000	84	84	2.24 (1.5)	
Region	Midwest	421	421	2.57 (2.09)	0.283
	South	480	478	2.36 (1.75)	
	West	365	365	2.65 (2.06)	
Number of medications	One	816	802	2.2 (1.76)	< 0.001
	Two	349	349	2.77 (1.99)	
	Three or more	182	180	3.47 (2.4)	

significantly with maximum duration of medication use, difficulties in access to care, and household income levels (Table 1). Increased side effects were observed with greater length of time using a medication, difficulty in access to mental healthcare or counseling, and household income <$50,000. Although side effects differed significantly by household income, no directional trend was observed.

A significant directional trend was observed in polypharmacy, our predictor of interest. On average, the number of side effects increased with the number of psychiatric medications being used. Further exploration of the type of side effects and severity levels associated with polypharmacy revealed decreased appetite, insomnia, and irritability to be the most commonly reported and parent-rated severe side effects among those taking one psychiatric medication (Table 2). However, the side effect profile of those taking three or more psychiatric medications shifted to irritability, sleepiness/fatigue, and increased appetite as the most commonly reported and severe side effects. Suicidality and self-harm per parent report also became more frequent with increasing numbers of medications used (Table 2).

Multivariable analysis of side effects

Significant positive association between polypharmacy and the number of side effects persisted in the model fully adjusted for all covariates (Table 3). Compared with subjects taking only one psychiatric medication, those taking two medications reported 17% (relative risk [RR] = 1.17) and those taking three or more medications reported 38% (RR = 1.38) increase in side effects on an average. The model assessing severity of the type of side effects revealed significant increase in odds of a parent-reported side effect being of moderate/severe intensity includes sleepiness/fatigue (odds ratio [OR] = 3.01), gastrointestinal upset (OR = 2.51), increased appetite (OR = 4.28), tics/tremors (OR = 4.48), thoughts of suicide (OR = 10.03) and intentional self-harm (OR = 4.66) with the use of three or more medications when compared with the use of one medication (Table 4). The significant effect of difficulties in access to care (RR = 1.42; OR of moderate/severe = 2.05) and household income levels persisted in both the models, whereas the effect of duration of longest medication use did not. Older subject age was also found to be associated with experiencing more side effects.

Table 2. Side Effect Intensity Levels by Number of Medications (Unadjusted for Covariates)

			Side effect intensity levels (%)		
Number of medications	*Type of side effect*	*Total with side effect (%)*	*Mild*	*Moderate*	*Severe*
One ($n = 803$)	Decreased appetite	46.33	30.14	13.7	2.49
	Insomnia	37.86	25.53	9.34	2.99
	Irritability	33.12	22.04	8.59	2.49
	Headaches	26.65	21.05	4.73	0.87
	Sleepiness or fatigue	23.05	18.56	3.24	1.25
	Gastrointestinal upset	16.07	12.58	2.99	0.5
	Increased appetite	15.94	9.46	5.11	1.37
	Tics or tremors	7.1	5.11	1.62	0.37
	Eye problems	4.85	3.61	1.12	0.12
	Thinking about suicide	4.36	3.99	0.25	0.12
	Intentional self-harm	3.86	2.74	0.87	0.25
	Problems with blood tests	0.36	0.12	0.12	0.12
Two ($n = 349$)	Decreased appetite	43.28	24.36	16.05	2.87
	Insomnia	41.26	23.21	14.33	3.72
	Irritability	42.7	26.65	11.75	4.3
	Headaches	25.79	20.63	4.3	0.86
	Sleepiness or fatigue	37.25	24.07	10.6	2.58
	Gastrointestinal upset	20.06	13.47	4.3	2.29
	Increased appetite	28.08	11.17	10.32	6.59
	Tics or tremors	10.61	8.6	2.01	0
	Eye problems	8.02	5.44	2.01	0.57
	Thinking about suicide	10.61	8.6	1.15	0.86
	Intentional self-harm	6.88	4.3	2.01	0.57
	Problems with blood tests	2.86	1.72	0.57	0.57
Three or more ($n = 180$)	Decreased appetite	31.67	17.78	12.22	1.67
	Insomnia	40.01	26.67	10.56	2.78
	Irritability	46.11	30	11.11	5
	Headaches	33.34	25.56	6.67	1.11
	Sleepiness or fatigue	45.56	30.56	10.56	4.44
	Gastrointestinal upset	31.67	20.56	8.33	2.78
	Increased appetite	43.34	15	17.78	10.56
	Tics or tremors	22.22	11.11	10	1.11
	Eye problems	8.89	6.67	2.22	0
	Thinking about suicide	18.89	13.33	5	0.56
	Intentional self-harm	17.78	11.11	6.67	0
	Problems with blood tests	7.23	6.67	0.56	0

Table 3. Adjusted Relative Risk Estimates of the Number of Side Effects

		Number of side effects		
Effect	*Level*	*RR*[a]	*95% CI*	p *value*
Number of medications[a]	One	1		
	Two	1.17	(1.06,1.29)	< 0.001
	Three or more	1.38	(1.23,1.56)	< 0.001
Age	age > 15	1		0.05
	12 < age ≤ 15	0.92	(0.82,1.03)	
	9 < age ≤ 12	0.93	(0.83,1.04)	
	age ≤ 9	0.84	(0.74,0.95)	
Gender	Female	1		0.08
	Male	0.92	(0.85,1.01)	
Race	White	1		0.80
	Nonwhite	1.02	(0.90,1.14)	
Maximum duration of any utilized medication	≤1 Year	1		0.32
	>1 Year	1.05	(0.96,1.15)	
Care access difficulties	No	1		< 0.001
	Yes	1.42	(1.30,1.55)	
Health insurance type	Some private health insurance	1		0.34
	No health insurance	0.8	(0.58,1.09)	
	Only public health insurance	0.97	(0.86,1.08)	
Household income	<$25,000	1		0.01
	$25,000 to $49,999	1.06	(0.92,1.22)	
	$50,000 to $74,999	0.84	(0.72,0.98)	
	$75,000 to $99,999	0.93	(0.78,1.09)	
	$100,000 to $149,999	0.86	(0.72,1.02)	
	>$150,000	0.85	(0.68,1.05)	
Region	Midwest	1		0.74
	South	0.97	(0.87,1.07)	
	West	1	(0.90,1.11)	

[a]Number of medications relative risk (RR) adjusted for other covariates in this table, reporting type 3 *p* values.

Table 4. Adjusted Odds Ratio (OR) for Side Effect Rating as Moderate or Severe

	Moderate or severe side effect rating			
Level	*Type of side effect*	*OR*[a]	*95% CI*	*Type 3* p *value*
One medication		1		
Two medications	Decreased appetite	1.01	(0.70, 1.44)	0.98
	Insomnia	1.25	(0.87, 1.81)	0.23
	Irritability	1.29	(0.87, 1.89)	0.21
	Headaches	0.86	(0.48, 1.55)	0.62
	Sleepiness or fatigue	2.86	(1.77, 4.62)	< 0.001
	Gastrointestinal upset	1.53	(0.84, 2.76)	0.16
	Increased appetite	2.42	(1.60, 3.67)	< 0.001
	Tics or tremors	0.86	(0.35, 2.12)	0.75
	Eye problems	1.39	(0.52, 3.70)	0.51
	Thinking about suicide	4.7	(1.20, 18.42)	0.03
	Intentional self-harm	2.01	(0.79, 5.11)	0.14
	Problems with blood tests	3.99	(0.73, 21.88)	0.11
Three or more medications	Decreased appetite	0.62	(0.37, 1.03)	0.07
	Insomnia	0.73	(0.42, 1.25)	0.25
	Irritability	1.19	(0.73, 1.94)	0.5
	Headaches	1.07	(0.54, 2.10)	0.85
	Sleepiness or fatigue	3.01	(1.74, 5.21)	< 0.001
	Gastrointestinal upset	2.51	(1.34, 4.69)	< 0.001
	Increased appetite	4.28	(2.70, 6.78)	< 0.001
	Tics or tremors	4.48	(2.20, 9.12)	< 0.001
	Eye problems	1.07	(0.29, 3.96)	0.91
	Thinking about suicide	10.03	(2.60, 8.76)	< 0.001
	Intentional self-harm	4.66	(1.89, 1.50)	< 0.001
	Problems with blood tests	1.79	(0.16, 19.99)	0.64

[a]OR derived from the generalized multivariate binomial model with side effect intensity relative to using one medication. Adjusted for covariates of age, gender, race, region of residence, maximum medication duration, care access difficulties, health insurance type, and household income.

In medication class-specific adjusted analyses, a 99% (RR = 1.99) increase in side effects was associated with the use of antipsychotics, and a 77% (RR = 1.77) increase was associated with the use of SSRIs when used in a combination with other medications versus when used alone (Table 5). Other medication classes contributed to cumulative polypharmacy side effects, but to a lesser degree.

Discussion

This study is the first, to our knowledge, to specifically explore the association between the number of psychiatric medications used by children and adolescents, and the number and severity of side effects they experienced. This side effect study is also unique in evaluating subjects who have used medications for a long period of time, rather than the 2 to 3 month time period typical of randomized controlled trials from which side effect frequencies in pharmaceutical product labeling are derived (PDR 2013; Harrington et al. 2011). Our approach has the advantage of characterizing ''real world'' use of medication, which is typically far longer than a few months, but has the disadvantage of missing data about any medications that caused side effects severe enough that the medications had to be discontinued prior to our query.

Within this cohort, adverse reactions were very commonly reported for psychiatric medications as a whole, with fewer than one in five subjects taking medications without any parent-observed side effects. As the number of medications increased, both the number and severity of side effects increased. After adjusting for covariates, the association of side effects to the number of medications remained both significant and sizeable (i.e., 38% more side effects attributable to taking three or more medications), and the likelihood that side effects would be rated as moderate or severe significantly increased (Tables 3 and 4).

Table 5. Adjusted Relative Risk Estimates of Side Effects with Polypharmacy for the Five Most Common Drug Classes

Drug class	n	*Relative risk*[a] *of side effects (poly vs. mono)*	*95% CI*	p *value*
Stimulants	863	1.11	(1.00, 1.24)	0.05
SSRIs	323	1.77	(1.46, 2.14)	≤0.001
Antipsychotics	249	1.99	(1.40, 2.84)	≤0.001
Mood stabilizers	183	1.25	(0.98, 1.59)	0.07
Central α agonists	174	1.26	(0.89, 1.79)	0.19

[a]All monotherapy versus polypharmacy models have been adjusted for age, gender, income group, type of insurance, and difficulty status in accessing mental health services.

SSRIs, selective serotonin reuptake inhibitors.

The clinical significance of this is that adverse effects of medication appear to accumulate with each additional medication prescribed, some more so than others. Increased appetite was 272% more prevalent among those using three or more medications than among those using one medication, and approximately four times as likely to be parent-identified as moderate or severe (Tables 2 and 3). This is clinically concerning because obesity and type 2 diabetes are long-term medical problems that could result from the use of psychiatric medications (Bobo et al. 2013). Sleepiness/fatigue was 198% more prevalent among those using three or more medications than among those using one medication, and approximately three times as likely to be rated as moderate or severe when present (Tables 2 and 3). This could be functionally impactful if medication-sedated youth are less engaged in school and other normal childhood and adolescent activities. Tics and tremors were 313% more prevalent among those using three or more medications. Because polypharmacy regimens often included tic-reducing medications (i.e., 42% received antipsychotics), this may mean that a subject with tic side effects from a medication such as methylphenidate may have been prescribed other medications, in part to treat that side effect.

Suicidal thoughts and self-harm are other areas of significant concern, as medications such as SSRIs have long been associated with some degree of suicidality (Hammad et al. 2006). This study was consistent with that finding, in that suicidal thoughts were 433% more prevalent and intentional self harm was 461% more prevalent among subjects using three or more medications versus those taking one medication. However, despite study parents' belief that these problems were potential medication side effects, it may have meant, instead, that subjects using multiple medications were more likely to have psychiatric problems such as severe depression, which caused their self-harm and suicidality. Regardless of the cause, this association means that clinicians may wish to pay extra attention to self-harm and suicidality among their patients receiving multiple medications.

Two medication groups were independently and significantly associated with a greater number of medication side effects (almost twice as likely) when their use was combined with other medications: The SSRIs and the antipsychotics. Because study subjects had extremely diverse individual treatment regimens, we are unable to identify the specific causes of either the SSRI or antipsychotic polypharmacy side effect risk elevation. However, one possible etiology is the same side effect being worsened through different but additive mechanisms, such as sedation from simultaneous anticholinergic, antihistaminic, and serotonin system changes. Also specific drug–drug interactions may augment changes to the same neurotransmitter system, such as SSRIs, stimulants, and antipsychotics, which are all known to increase serotonin levels (Micromedex 2013). However, we caution against interpreting increased side effect risk in polypharmacy as only isolated to SSRIs and antipsychotics, because each medication class had a positive trend toward a greater number of side effects when it was used was in combination, the significance of which may have been influenced by sample size (Table 5). For example, stimulants were weakly clinically associated ($RR = 1.1$, $p = 0.05$) with greater side effects in the setting of polypharmacy, but as a majority of participants were using stimulants, the statistical power for detecting differences within this group was far greater than with other medications.

Parents who reported that they had experienced difficulty in accessing care for their child were also more likely to report that there were side effects (i.e., 42% increased risk of side effects). This care access difficulty could mean a belief that their children were receiving care of low quality or had inadequate access to follow-up appointments, and/or inadequate access to providers of a desired specialty. Parent-perceived poor access to desired counseling may have led to increased side effects via a greater therapeutic reliance on medications and at higher dosages relative to those with adequate access to counseling. Perceived poor access to a preferred prescribing provider may have led to poorly monitored medication titration plans, yielding greater numbers of side effects.

The CPES design of asking parents for their observations about their children is both an advantage and a limitation. The advantage is that parents typically are the primary evaluators of their child's symptoms, provide consent for medication use, and are the information source in other child psychiatric research (Achenbach and Rescorla 2001; Becker et al. 2004; Bufferd et al. 2011). On the other hand, because the children themselves were not interviewed in this study, information is limited to parent report, and parent interpretation that side effect symptoms were caused by medication rather than by underlying disorders. Significant correlations are also not proof of causation.

Additional limitations include the low survey response rate, which may reflect a self-selection bias (Asch et al. 1997). This limitation is mitigated by demographic similarities between invited and respondent populations, which indicates that our sample was generally representative of the target population. Another limitation is that none of the respondents were from the Northeast, where prescribing practices might differ. And in the case of preenrollment medication stops because of intolerance, findings may have also underestimated medication side effects.

These limitations notwithstanding, we present findings that are previously unreported and difficult to research using existing national data sets or insurance claims files. Although we cannot assert that our findings are generalizable to all children and adolescents using psychiatric medication, they do add to the sparse literature on pediatric psychotropic polypharmacy.

Conclusions

Children and adolescents using psychiatric medications very commonly experienced side effects. Those with difficulty in accessing care and using greater numbers of psychiatric medications experienced an overall greater parent-reported side effect burden (including increased appetite, sedation, tics, self-harm, and

suicidality), particularly if the medication combination included SSRIs or antipsychotics. Future research is needed to replicate these findings in other samples, and to investigate if side effects can be reduced by a clinically appropriate minimizing of the number of medications utilized within a psychiatric polypharmacy regimen, or by assuring that children and adolescents using psychiatric medications have adequate access to skilled healthcare providers.

Clinical Significance

This study reports psychiatric medication side effect experiences in an exploratory analysis among children and adolescents from diverse economic, insurance, and geographic regions. Among these children and adolescents who use psychiatric medications, a pattern of increasing side effect occurrence and severity was found with an increasing number of medications utilized, with polypharmacy including SSRIs or antipsychotics, and with parent-perceived limited access to care.

Disclosures

Bryan King reports serving as a consultant to Roche and Seaside Therapeutics. He is on the scientific advisory board of Confluence Therapeutics and the Autism Science Foundation. He has received or has pending research grant support from Seaside Therapeutics, Roche, and Novartis. The other authors have no competing financial interests.

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