Polypharmacy in Children and Adolescents Treated for Major Depressive Disorder: A Claims Database Study

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Objective: To describe the rate and trajectory of change in psychiatric polypharmacy during the past decade in children and adolescents treated for major depressive disorder.

Method: Data from the South Carolina Medicaid program covering outpatient and inpatient medical services and medication prescriptions from January 1996 through December 2005 were procured for the analysis herein. We examined pharmacotherapy patterns for 1544 children and adolescents diagnosed with major depressive disorder using DSM-IV criteria.

Results: A rapid upward trajectory in the rate of psychiatric polypharmacy (i.e., ≥ 2 psychotropic medications) was noted ($\chi^2 = 810.46$; $p < .0001$), with the greatest velocity of change between 1997 and 2003. The likelihood of being prescribed conventional unimodal antidepressants decreased significantly between 2001 and 2005 ($\chi^2 = 831.06$; $p < .0001$). Non–African Americans and males were 1.27 times more likely to be prescribed a polypharmacy regimen, as were those with additional psychiatric disorders, especially attention-deficit/hyperactivity disorder (OR = 2.58), bipolar disorder (OR = 1.87), and psychotic disorders (OR = 1.74). Individuals with a substance use disorder were less likely (OR = 0.86) to be prescribed a polypharmacy regimen. The likelihood of being prescribed psychiatric polypharmacy increased as a function of the number of additional psychiatric disorders ($\chi^2 = 798.22$; $p < .0001$).

Conclusion: Psychiatric polypharmacy is both prevalent and increasing in pediatric populations, in tandem with the greater diagnostic complexity (multiple disorders) of those treated. Simultaneously, practitioner reliance on conventional unimodal antidepressants has been decreasing, a trend that began prior to the U.S. Food and Drug Administration warnings regarding their potential for increasing the risk of suicidality.

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The prevalence of mood and behavioral disorders among children and adolescents has increased significantly during the past 2 decades. For example, attention-deficit/hyperactivity disorder (ADHD), major depressive disorder (MDD), bipolar disorder, and behavioral disorders accompanied by psychotic and violent features are frequently identified as disorders that necessitate clinical intervention in pediatric populations.[1–4] Changing diagnostic patterns reflect several factors, including, but not limited to, differences in diagnostic nosology, health service accessibility and utilization, and available treatments.[5]

Similar to practices in adult populations, therapeutic regimens composed of more than 1 psychotropic agent (i.e., polypharmacy) are increasingly encountered in the outpatient management of pediatric psychiatric disorders in both public and private service systems.[6–9] For example, results from pharmacoepidemiologic studies indicate that approximately 23% to 42% of pediatric populations utilizing psychiatric services are receiving a polypharmacy regimen. The combination of antipsychotics with psychostimulants, traditional mood

stabilizers, and conventional unimodal antidepressants is frequently employed when managing mood, behavioral, neuropsychiatric, and psychotic disorders.[10] Factors preliminarily associated with polypharmacy are race (i.e., less likely to be Hispanic or African American), age, and guardianship status.[11,12]

Notwithstanding the common practice of polypharmacy, the evidentiary base informing treatment decisions related to the prescription of multiple psychiatric medications in young populations is woefully inadequate. Recent U.S. Food and Drug Administration (FDA) public advisories and "black-box" labeling of product inserts for conventional unimodal antidepressants have intensified interest in the safety profile of conventional antidepressant therapy and provided the impetus for possibly increased use of alternative medication approaches. Since the initial public advisory in 2004 regarding conventional antidepressants, there have been several reports of decreasing use of this class of agents.[13]

The encompassing aim of the analysis herein was to describe the rate and trajectory of change in psychiatric polypharmacy during the past decade in children and adolescents treated for MDD in a publicly funded system. We had 4 interrelated hypotheses: (1) the rate of polypharmacy would be greater in proximal when compared to distal years of observation, (2) the rate of polypharmacy would be closely associated with the presence of comorbid psychiatric disorders, (3) atypical antipsychotics would be more frequently prescribed, and (4) there would be a contemporaneous decrease in the use of conventional unimodal antidepressants.[5,12,13]

METHOD

Claims data for the South Carolina Medicaid program were obtained through the state's Office of Research and Statistics. Data from both medical and pharmacy claims were used, with encrypted patient demographics and identifiers to protect patient confidentiality. Each Medicaid medical claim identifies a service encounter and gives the date of service and the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) diagnosis codes related to that visit (visit file). Pharmacy claims identified the medication dispensed and the date the prescription was filled (pharmacy file). A separate data file regarding eligibility was used to summarize the demographics for each patient (person file). The databases are frequently updated prior to being made available for analysis. This study was approved by the University of South Carolina Institutional Review Board as exempt from human subject research guidelines under 45 Code of Federal Regulations part 46.

Medical and pharmacy claims for the calendar years January 1, 1996, through December 31, 2005, were used to identify a cohort of child and adolescent individuals (aged 17 and under) eligible for Medicaid for a minimum of 9 months in each calendar year included in this analysis who had a service encounter and who were diagnosed with MDD on at least 1 service visit. The pharmacy records for the children and adolescents in this cohort were then analyzed. The dates of interest (i.e., 1996–2005) were chosen as this epoch corresponded with an expansion of FDA-approved agents for mood disorders (e.g., atypical antipsychotics) as well as a rising diagnosis rate for bipolar disorder and other disorders in children and adolescents.[1–3]

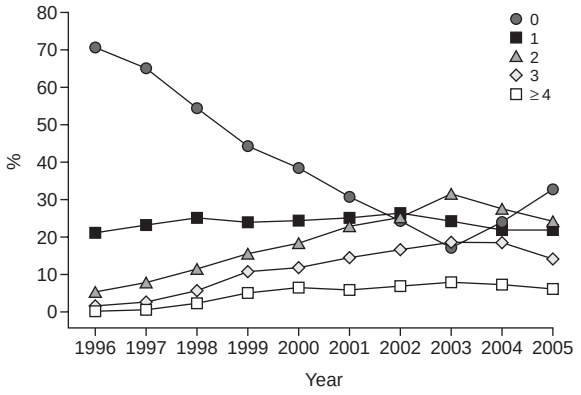
Statistical Analysis

Descriptive analyses were performed to identify the numbers of young individuals in the data set prescribed 0 to ≥ 4 psychotropic medications during each year examined and to portray the most typical combination patterns characteristic of each year. A general linear regression model was used to fit the data with maximum likelihood estimation (PROC GENMOD; SAS Institute Inc., Cary, N.C.) to assess the relative odds associated with being prescribed multiple psychotropic medications, using 9 years of the study data as repeated measures, the duration of treatment with an antidepressant, and type and number of additional psychiatric conditions requiring the psychotropic medications as the main independent variables and controlling for 3 individual demographic factors (i.e., gender, ethnicity, and age), dichotomously coded as male/female, African American/ other, and other children (aged ≤ 12 years)/adolescents (aged ≥ 13 years) at initiation of antidepressant medication.

In order to determine if there were differences over time in the duration of prescriptions of each class of psychotropic agents, the new individuals admitted in each year of the data file from 1996 to 2003 were identified and the total number of prescriptions/refills of 4 classes of medications during their tenure in the data file (1996–2005) were calculated for each case: antipsychotics, antidepressants, mood stabilizers, and psychostimulants. No new admissions to the cohort were analyzed for 2004 and 2005 to allow 24 months of available follow-up for those newly admitted in 2003. A least-squares general linear regression analysis was then performed using the total number of prescriptions per class of medications (total for antipsychotics, antidepressants, mood stabilizers, and psychostimulants) as the dependent variables and time as the independent variable in each equation.

Finally, in order to determine if there were differences over time in the proportion of individuals prescribed antidepressants, the individuals prescribed antidepressants in each year of the study were identified and a multiple logistic regression analysis performed with "prescribed antidepressants or not" as the dependent variable and each year of the study as an independent variable (1996 compared to 1997–2005).

Figure 1. Number of Medications Prescribed Over Time



RESULTS

Patients

The demographics of this MDD cohort (N = 1544) were 57.3% female, 39.1% African American and 56.4% white, and 54.1% aged 13 years or older (adolescents) when their antidepressant medication was initiated. Sixty-two percent of the cohort were diagnosed as having MDD only (no other psychotic or affective disorders noted), but the following disorders were also coded for the remaining 38%: schizophrenia (N = 103, 6.7%), schizoaffective disorder (N = 71, 4.6%), bipolar disorder (N = 496, 32.1%), and other psychotic disorders (N = 243, 15.7%). Moreover, 1015 (65.7%) were diagnosed with conduct disorder/oppositional defiant disorder, while 907 (58.7%) had ADHD, 712 (46.1%) had organic brain syndrome or severe mental retardation, and 401 (26.0%) had a substance use disorder coded at some visit during their tenure in the Medicaid system.

Figure 1 presents the percentage of young individuals prescribed 0 to ≥ 4 medications on an annual basis during the 10-year study period. The number of individuals prescribed ≥ 2 psychotropic medications climbed steadily over time from 1996 (7.9%) to 1997 (11.3%), 1998 (20.0%), 1999 (31.4%), 2000 (37.0%), 2001 (43.7%), 2002 (49.3%), and 2003 (58.1%), with a slight decline in the years 2004 (53.6%) and 2005 (44.8%).

Table 1 presents the results of the logistic regression using number of psychotropic medications prescribed as the dependent variable and modeling type of additional mental disorder. The effect across years was significant, confirming that, between 1997 and 2003, youths with MDD as one of their diagnoses were significantly more likely to be prescribed multiple psychotropic medications. This likelihood increased between 1996 and 2005, with the highest OR noted between 1997 (OR = 1.37) and 2003 (OR = 17.19) compared to 1996. Non–African Americans were 1.28 times more likely to be prescribed combined pharmacotherapy, as were males and those with other psychiatric disorders, especially ADHD, bipolar disorder, and psychotic disorders. Those with substance use disorders were less likely to be prescribed multiple psychotropic medications.

In a separate logistic regression modeling the number of diagnosed disorders from 1 to 6, the likelihood of being prescribed more psychotropic medications increased as the number of diagnosed psychiatric conditions/disorders increased from 1 (OR = 1.45, 95% CI = 1.20 to 1.74), to 2 (OR = 2.40, 95% CI = 2.02 to 2.86), 3 (OR = 4.64, 95% CI = 3.89 to 5.54), 4 (OR = 6.77, 95% CI = 5.56 to 8.23), 5 (OR = 10.20, 95% CI = 7.98 to 13.03), and 6 (OR = 9.80, 95% CI = 6.97 to 13.77) ($\chi^2 = 798.22$; $p < .0001$) compared to those with MDD only (i.e., no psychotic or other affective conditions diagnosed) (OR = 0.40; 95% CI = 0.35 to 0.45) when controlling for annual, age, gender, and ethnic differences.

Table 2 presents the percentage of individuals in which the medications were prescribed concomitantly or were switched for each year of the study period. There was a steady increase from 1996 (6.7%) through 2005 (41.6%) in the percentage of individuals receiving concomitantly prescribed medications. The majority of individuals who were coded as having their medication treatment "switched" discontinued the index antidepressant and changed to an alternative antidepressant, i.e., from tricyclic antidepressants (TCA) to selective serotonin reuptake inhibitors (SSRIs) in 1996 and 1997 and from SSRIs to serotonin-norepinephrine reuptake inhibitors (SNRIs) between 1998 and 2005. The composition of the polypharmacy regimens differed as a function of the year of observation, i.e., disparate antidepressants with a psychostimulant (1996–2001); antipsychotics with SSRIs (1998); antipsychotics with traditional mood stabilizers and various antidepressants (2000–2001); and antipsychotics co-prescribed with SSRIs, mood stabilizers, or psychostimulants (2002–2005).

A comparison of prescription duration for antipsychotics, antidepressants, mood stabilizing medications, and psychostimulants is presented in Table 3. The mean length of time antipsychotics were prescribed trended downward as a function of time. Most of the children who were prescribed an antipsychotic agent remained on treatment for a mean duration of 1 year. Antidepressants were initially prescribed for these pediatric individuals for more than 3-year periods, but this decreased to a mean duration of less than 2 years over time, representing a consistent and statistically significant trend. Similarly, the duration of mood stabilizer usage significantly decreased by approximately 50% during the time period examined (i.e., from approximately 12–16 months to 8–10 months). The duration in use of psychostimulants also significantly decreased from a mean of approximately 3 years for those newly admitted in the mid-1990s to a mean of

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Table 1. Adjusted Odds Ratios for Polypharmacy Among Adolescents With Major Depressive Disorder by Time, Risk Factors, Treatment Duration, and Comorbid Psychiatric Disorders

Variable	df	χ^2	p	Odds Ratio	95% CI
Year	9	810.46	< .0001		
1997–1996				1.37	1.19 to 1.57
1998–1996				2.48	2.12 to 2.90
1999–1996				4.54	3.86 to 5.33
2000–1996				6.41	5.42 to 7.59
2001–1996				9.02	7.58 to 10.73
2002–1996				12.23	10.23 to 14.62
2003–1996				17.01	14.18 to 20.41
2004–1996				13.37	11.12 to 16.07
2005–1996				8.91	7.38 to 10.74
African American	1	19.12	< .0001	0.78	0.70 to 0.87
Male	1	15.80	< .0001	1.27	1.13 to 1.42
Duration of treatment	1	35.79	< .0001	1.40	1.26 to 1.56
Psychotic disorder	1	48.27	< .0001	1.74	1.51 to 2.00
Bipolar disorder	1	96.19	< .0001	1.87	1.66 to 2.10
ADHD	1	169.05	< .0001	2.58	2.28 to 2.91
CD/ODD	1	41.97	< .0001	1.50	1.33 to 1.69
Organic brain syndrome, MR	1	29.94	< .0001	1.37	1.23 to 1.53
Substance use disorder	1	6.54	.01	0.86	0.77 to 0.97

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CD = conduct disorder, MR = mental retardation, ODD = oppositional defiant disorder.

Table 2. Changes in Polypharmacotherapy Medications Over Time

Year	Concomitant, %	Switched, %	Most Frequent Type of Co-Prescription Patterns
1996	6.7	2.2	TCA + stimulant, mood stabilizer + stimulant, SSRI-SNRI, SNRI + stimulant, antipsychotic + stimulant
1997	9.7	3.6	TCA + stimulant, mood stabilizer + stimulant, SSRI + stimulant, SNRI + stimulant, SSRI-SNRI
1998	17.0	6.8	SSRI-SNRI, SSRI-SNRI + TCA, mood stabilizer + stimulant, TCA + stimulant, SNRI + stimulant, antipsychotic + stimulant, antipsychotic + SSRI
1999	28.5	9.5	SSRI-SNRI, SSRI + stimulant, antipsychotic + SSRI-SNRI, SSRI-SNRI + stimulant, SNRI + stimulant, antipsychotic + stimulant, antipsychotic + SSRI
2000	31.8	10.4	SSRI-SNRI, antipsychotic + mood stabilizer, antipsychotic + SSRI, antipsychotic + SSRI-SNRI, SNRI + stimulant, SSRI + stimulant, mood stabilizer + stimulant
2001	41.6	8.0	SSRI-SNRI, SSRI-SNRI + stimulant, SSRI + stimulant, antipsychotic + mood stabilizer, antipsychotic + SSRI, SNRI + stimulant, antipsychotic + SSRI-SNRI
2002	45.8	11.1	SSRI-SNRI, antipsychotic + SSRI, SSRI + stimulant, SNRI + stimulant, antipsychotic + SNRI, antipsychotic + SSRI-SNRI, antipsychotic + SSRI + stimulant
2003	53.9	14.2	SSRI-SNRI, antipsychotic + SSRI, SNRI + stimulant, SSRI + stimulant, antipsychotic + SNRI, antipsychotic + SSRI-SNRI, antipsychotic + SSRI-SNRI + stimulant, antipsychotic + stimulant, SSRI-SNRI + stimulant
2004	49.7	12.9	SSRI-SNRI, SNRI + stimulant, SSRI-SNRI + stimulant, SSRI + stimulant, antipsychotic + SSRI, antipsychotic + SNRI, antipsychotic + stimulant, antipsychotic + SSRI-SNRI, antipsychotic + SSRI + mood stabilizer, antipsychotic + SSRI + stimulant
2005	41.6	8.8	SSRI-SNRI, SNRI + stimulant, SSRI + stimulant, antipsychotic + SSRI, antipsychotic + SNRI, antipsychotic + mood stabilizer, antipsychotic + stimulant, antipsychotic + SSRI-SNRI

Abbreviations: SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Table 3. Least Squares Mean (SD) Prescription Duration for Newly Admitted Patients in Each Year for 4 Classes of Psychotropic Medications (in months)

Year	Antipsychotics	Antidepressants	Mood Stabilizers	Psychostimulants
1996	22.88 (50.73)	40.82 (54.19)	16.41 (37.65)	34.67 (63.17)
1997	21.93 (52.91)	31.78 (41.24)	14.80 (35.57)	18.43 (33.29)
1998	15.83 (31.80)	30.45 (40.61)	9.47 (26.59)	15.63 (32.54)
1999	17.02 (39.28)	32.89 (39.55)	9.50 (22.26)	10.40 (18.96)
2000	13.98 (27.38)	34.31 (53.40)	6.30 (13.20)	16.64 (32.44)
2001	5.00 (10.25)	20.57 (19.87)	8.34 (27.33)	11.62 (25.65)
2002	15.90 (37.25)	29.97 (49.76)	10.48 (27.26)	7.93 (21.07)
2003	7.50 (10.32)	22.67 (18.52)	3.83 (10.11)	2.25 (3.91)
F Statistic	1.92	2.70	2.54	8.99
p Value	.06	.008	.01	< .0001

Table 4. Adjusted Odds Ratios for Being Prescribed Antidepressants Over Time

Source	df	χ^2	p	Odds Ratio	95% CI
Year	9	831.06	< .0001		
1997–1996		62.00	< .0001	1.57	1.40 to 1.76
1998–1996		133.03	< .0001	2.22	1.94 to 2.54
1999–1996		41.29	< .0001	0.47	0.33 to 0.61
2000–1996[a]				0.14	
2001–1996		12.14	.0005	0.76	0.65 to 0.89
2002–1996		61.22	< .0001	0.52	0.45 to 0.62
2003–1996		184.61	< .0001	0.29	0.25 to 0.35
2004–1996		298.66	< .0001	0.12	0.09 to 0.15
2005–1996		297.38	< .0001	0.09	0.07 to 0.12

[a]There were no significant differences between the years 1996 and 2000.

approximately 2 months for those newly admitted in 2003.

Finally, there was a similar trend in the reduction over time in the proportion of individuals prescribed antidepressants (Table 4). When compared to the level of antidepressant use in 1996, the increasing use of antidepressants was most pronounced between 1997 and 1998, with slower upward growth in 2000 and reaching an asymptote in 2001, followed by a downward trajectory of use between 2002 and 2005.

DISCUSSION

The majority of individuals in the cohort were diagnosed with MDD only and had their medication treatment switched from the index antidepressant to a newer antidepressant over the course of their treatment. Simultaneously, the use of multiple psychotropic medications became common practice during the epoch 1996 to 2005, primarily in relation to the diagnosis of multiple psychiatric conditions (38% of the cohort), in this Medicaid-covered pediatric population.

Moreover, an annualized increase in the rate of concomitant polypharmacy was noted between 1996 (6.7%) and 2005 (41.6%). A significant linear relationship between the number of additional conditions and the probability of psychiatric polypharmacy was noted, with the exception of substance use disorders, wherein an inverse relationship was noted. The positive relationship between number of diagnosed psychiatric conditions and the use of combination pharmacotherapies could be expected in the context of the treatment guidelines for each of the additional disorders published during this epoch.[14–16] However, the inverse relationship of combination pharmacotherapies and the presence of substance use disorders does not comport with available research demonstrating that comorbid substance use disorders do not improve without specific treatment and that lithium, some SSRIs, atomoxetine, and bupropion have produced significant improvements in adolescents with comorbid ADHD or mood disorders and substance use disorders.[17] We speculate that only the primary psychiatric conditions were being medicated because community practitioners were less familiar with the treatment of comorbid substance use disorders.

Furthermore, we observed an annualized decreased initiation and duration of use of prescribed antidepressants between 2002 and 2005. The duration of use of mood stabilizers also decreased (approximately 50%) as did the duration of use of psychostimulants (i.e., by approximately two thirds) during the epoch investigated. While the annualized initiation and duration of antipsychotic prescriptions also decreased over time, no clear, linear trend was evident.

The demographics of this cohort differ from those in another cohort previously noted to be diagnosed with MDD.[14] Instead of demonstrating a 1:2 ratio in male/female and in children/adolescents, our cohort was only 57% female and 54% adolescent. The difference may reflect the inclusion of comorbid or additional disorders rather than MDD-only individuals. Non–African Americans were significantly more likely to be prescribed multiple psychiatric medications, as were males and those with additional psychiatric disorders, especially ADHD, bipolar disorder, and psychotic disorders. The effect of race and gender on polypharmacy in our study coheres with results previously published by other groups, with males or nonethnic pediatric patients being more likely to receive psychotropics, alone or in combination.[8,11,18]

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Our findings provide empirical evidence that practitioner prescribing patterns (proportion and duration) for the major classes of psychotropic medications (notably antidepressants) significantly changed in the years prior to, and ultimately coincided with, the FDA public warnings regarding antidepressants. Since the FDA warnings were not issued until 2003/2004, practitioners were changing their prescribing practices prior to the FDA pronouncements; undoubtedly, the public warning provided further impetus for decreasing utilization of conventional unimodal antidepressants.[13,19,20]

These practice patterns may also be the consequence of several related secular trends during the epoch investigated. There was increased availability and widespread marketing of nontraditional antidepressants (e.g., atypical antipsychotics) during a period when practitioners were diagnosing more psychotic/aggressive/violent features or disorders in their young patients. Patients with these more severe illness presentations (e.g., comorbidity) were more frequently diagnosed between 1996 and 2005, providing the clinical basis for changing the types and number of medications used. There was also increased evidence for the use of atypical antipsychotics as mood stabilizers and as an augmentation strategy for treatment-resistant depression during the epoch examined.[15] Finally, without a clear evidentiary base to rely on,[14,20] practitioners had to attend to the individual patient tolerability and safety issues associated with changing prescription patterns for the prescribed agents or groups of agents. Our results demonstrate that these practitioners met the clinical challenges posed to them in changing and complex diagnostic presentations by using the ever-changing pharmacopoeia available.

There are several methodological issues which limit inferences and interpretations that can be drawn from our findings using an administrative, rather than clinical data set: (1) the diagnosis of MDD and any additional mental disorders was not confirmed with a structured clinical interview; (2) the coding system allowed for individuals to receive a diagnosis of both MDD and bipolar disorder, but, since this is a longitudinal data set, we assumed without further analysis that these were sequential rather than concomitant diagnoses of evolving conditions (i.e., participants were initially diagnosed with MDD and subsequently were diagnosed with bipolar disorder); and (3) the results of the data primarily generalize to young populations utilizing a public service system, and extrapolations to other populations in private service settings may not be warranted.

Notwithstanding the limitations enumerated, the results from this ecological data set are illuminous and harmonize with clinical experience. Specifically, the prescription of a polypharmacy regimen in this pediatric mood disorder population is increasing and has become common practice. Coinciding with the rapid expansion of the available pharmacopoeia and the increasing prevalence of select pediatric psychiatric disorders, atypical antipsychotic use in combination with other psychotropic agents has increased. Converging with other recent reports, a downward trend in the use of conventional unimodal antidepressants during the past 5 years has occurred.[15,16]

Taken together, it appears that young populations with MDD and additional disorders are receiving updated and increasingly broad regimens of pharmacotherapy, both FDA approved and FDA unapproved, for the management of their mood syndromes and additional psychotic and behavioral disorders, which comports with the practice parameters released during this epoch. Replication and extension of these results using controlled trial methods are required before stronger pronouncements are made regarding the implications of these findings. In the interim, clinicians should endeavor to ensure that young populations are receiving guideline-concordant care for their mood and related disorders, and research efforts should attempt to further evaluate the therapeutic index of existing combination treatments in representative populations and the efficacy and safety of newer medications (e.g., the use of extended-release methylphenidate or atomoxetine) in pediatric patients with comorbid disorders.

Drug names: atomoxetine (Strattera), bupropion (Aplenzin, Wellbutrin, and others), lithium (Eskalith, Lithobid, and others), methylphenidate (Daytrana, Ritalin, and others).

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