I. Executive Summary

ACS-Heritage conducted an in-depth analysis of psychotropic drug use among patients under the age of 18. Three specific drug classes were chosen for review. A review of stimulants, antidepressants, and antipsychotics was performed to determine utilization among this population. The findings include the following:

- Stimulants are the most utilized psychotropic agents among patients under the age of 18.
- Approximately 23,183 patients received a claim for an antidepressant agent. Of these, nearly 75% of the claims were for an agent referenced in the March 2004 warning letter issued by the FDA.
- Data analysis showed that 19,403 patients received a claim for an antipsychotic agent. Of these, nearly 98% of the claims were for an atypical antipsychotic, which has no FDA-approved indication for children under the age of 18.
- Approximately 19,365 or 31% of the patients identified has two or more of the three drugs selected.
- Twenty-eight percent (28%) or 12,335 of the patients receiving stimulants do not appear to have a proper diagnosis warranting their use.
- Fifty-two percent (52%) or 12,168 of patients receiving antidepressants do not appear to have a proper diagnosis warranting their use.
- Forty-seven (47%) or 9,115 of patients receiving antipsychotics do not appear to have a proper diagnosis warranting their use.
- Inappropriate dosing among agents within each drug class revealed that 52% of antipsychotics, 14% of stimulants, and 10% of antidepressant doses were potentially administered inappropriately.

II. Background

At the request of Texas Health and Human Services Commission, ACS-Heritage conducted an in-depth analysis evaluating drug utilization among patients under the age of 18. The specific drugs evaluated are part of three different drug classes. All agents among stimulants, antidepressants, and antipsychotics were selected for review. An analysis was also performed evaluating clinical issues such as inappropriate drug use (based on documented diagnosis), inappropriate dosing, and combination therapy. Age and gender demographics were also isolated. Issues related to overutilization among prescribers was also performed and included in the analysis. The retrospective review of claims was conducted for July and August 2004.

In March 2004, the U.S. Food and Drug Administration (FDA) requested that manufacturers of several antidepressant drugs include within their labeling a warning statement recommending close observation of adult and pediatric patients treated with their agents for worsening of depression and/or emergence of suicidal ideations. The drugs of concern are highlighted below:

- Prozac® (fluoxetine)
- Zoloft® (sertraline)
- Paxil® (paroxetine)
- Celexa® (citalopram)
- Lexapro® (escitalopram)
- Effexor® (venlafaxine)
- Remeron® (mirtazapine)
- Wellbutrin® (buproprion)
- Luvox® (fluvoxamine)
- Serzone® (nefazodone)

Initial studies with Paxil® (paroxetine) and subsequent studies with other agents suggest that there appears to be an increased risk of suicidal thought and actions in children who were prescribed antidepressant drugs. Several of these drugs are also approved for the treatment of obsessive-compulsive disorder (OCD) in pediatric patients (sertraline, fluoxetine, fluvoxamine). Only Prozac® (fluoxetine) is approved for use in children with major depressive disorder. The rest of the drugs have no FDA approved uses in children.

Although it is unclear whether antidepressants directly contribute to the emergence of suicidal thinking and behavior, the FDA's actions are intended to highlight the need for careful monitoring of patients, particularly children and adolescents being treated with these drugs. Therapy changes should be conducted under the guidance of a physician, as certain medications should be

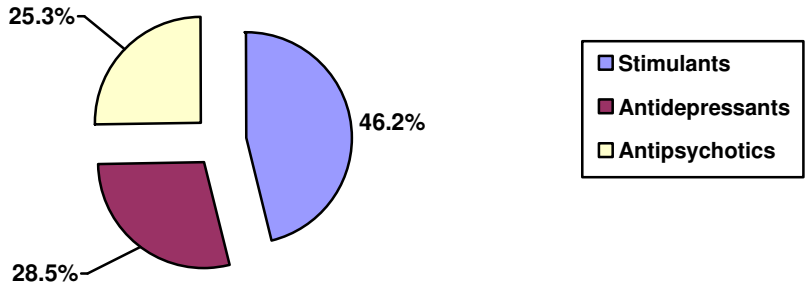
tapered rather than stopped abruptly. Following these suggestions, the FDA recently endorsed the advisory committee's recommendations regarding reports of an increased risk of suicide associated with the use of antidepressants in children. The following recommendations were made:

- FDA endorsed an approach to classify and analyze all suicidal events and behaviors observed in controlled clinical trials.
- Concluded that the findings of an increased risk of suicide applied to all the drugs studied as well as agents not included in controlled clinical trials in pediatric patients.
- Reached a split decision regarding recommending a "black-box" warning related to an increased risk for suicide in pediatric patients for all antidepressant drugs.
- Endorsed a patient information sheet for antidepressants to be provided to the patient or his/her caregiver with every prescription.
- Recommended that the results of controlled pediatric trials of depression be included in the labeling for antidepressant drugs.

The availability of atypical antipsychotics with a more favorable side effect profile when compared to older typical agents has increased their utilization among children with behavior disorders. Many of the atypical antipsychotics such as Zyprexa® (olanzapine), Risperdal® (risperidone), and Clozaril® (clozapine) have been studied in children suffering from various illnesses such as Tourette's syndrome, bipolar mania, autism, anorexia, schizophrenia, and other pervasive developmental disorders. Most of these studies have been small in scale and provided minimal background on the use of these agents in children and adolescents. Additional studies are needed to define ideal dosing strategies and long-term safety of these agents in younger patients. Currently, no atypical antipsychotics are approved for use in children.

Various analyses reveal that the amount of stimulant prescriptions written for children is on the rise. Although stimulants are approved for the use in children over three years of age, concerns of adverse drug events have persisted for this patient population. Studies have documented a widespread use of these agents for non-FDA approved indications. A consensus exists that behaviorally disturbed children are increasingly subjected to pharmacological agents as opposed to informed and coordinated psychotherapeutic options.

Psychotropic Drug Use Among Patients under 18 years of age

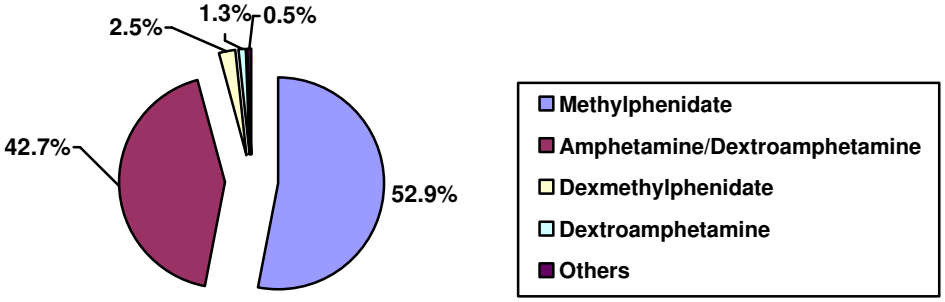


Psychotropic Drug Summary Report (July – August 2004)

Drug Class	*Patients*	*Claims*	*Percent of Claims*	*Total Paid*	*Paid per Claim*
Stimulants	43,523	66,871	46.2%	$6,551,603	$97.97
Antidepressants	23,187	41,292	28.5%	$2,461,835	$59.62
Antipsychotics	19,404	36,547	25.3%	$8,272,432	$226.35
TOTALS	*86,114*	*144,710*	*100%*	*$17,285,871*	*$119.45*

As expected, stimulants were the most prescribed psychotropic drug class among patients under 18 years of age. This is due to their documented efficacy in the treatment of hyperactivity disorders and approved FDA-labeling. A spreadsheet listing all patients identified is presented in Exhibit 1.

Stimulant Drug Use Among Patients under 18 years of age

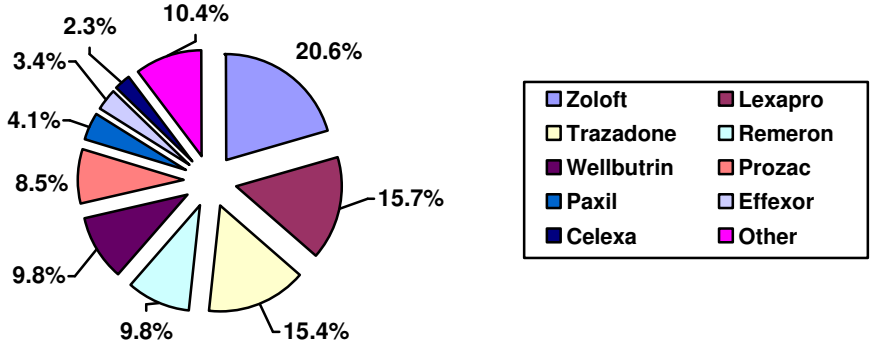


Stimulant Drug Summary Report (July – August 2004)

Drug Class	*Patients*	*Claims*	*Percent of Claims*	*Total Paid*	*Paid per Claim*
Methylphenidate	23,592	35,357	52.8%	$3,429,073	$96.98
Amph/Dextroamph	18,943	28,574	42.7%	$2,893,048	$101.25
Dexmethylphenidate	1,208	1,707	2.5%	$98,976	$57.98
Dextroamphetamine	609	893	1.3%	$31,853	$35.67
Others	237	337	0.5%	$49,111	$207.22
TOTALS	*44,589*	*66,868*	*100%*	*$6,502,061*	*$97.24*

Methylphenidate products such as Concerta®, Ritalin®, and Metadate® were the most prescribed stimulants. This group was followed by the combination of dextroamphetamine/amphetamine salts such as Adderall®. Dexmethylphenidate (Focalin®) and dextroamphetamines (Dexedrine®) were prescribed to nearly 4% of the population. "Other" agents such as Cylert® (pemoline), Provigil® (modafanil), and caffeine products were given to less than 1% of the study population.

Antidepressant Drug Use Among Patients Under 18 Years of Age

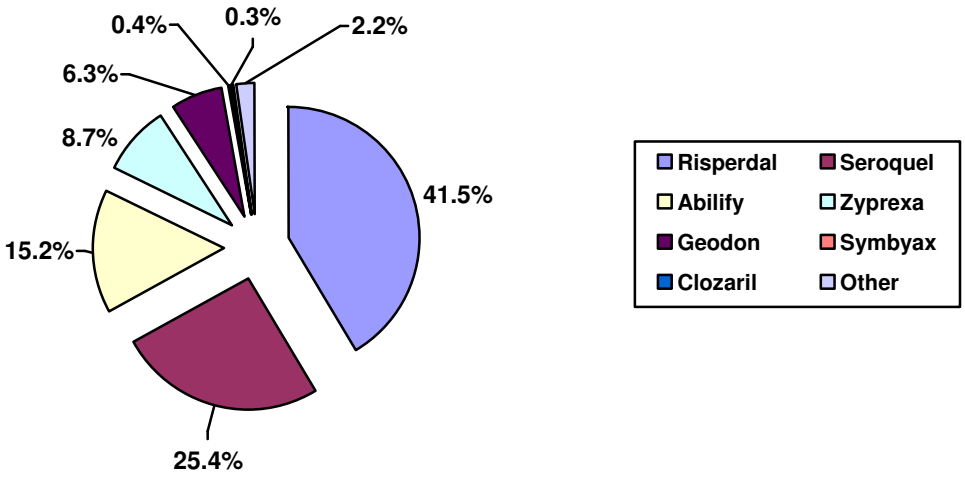


Antidepressant Drug Summary Report (July – August 2004)

Drug Class	*Patients*	*Claims*	*Percent of Claims*	*Total Paid*	*Paid per Claim*
Zoloft® (sertraline)	5,481	8,507	20.6%	$731,150	$85.95
Lexapro® (escitalopram)	4,180	6,486	15.7%	$444,468	$68.42
Desyrel® (trazodone)	4,068	6,347	15.4%	$51,904	$8.18
Remeron® (mirtazapine)	2,579	4,042	9.8%	$264,123	$65.34
Wellbutrin® (buproprion)	2,563	4,053	9.8%	$374,421	$92.38
Others (TCAs)	2,826	4,025	8.8%	$65,851	$23.30
Prozac® (fluoxetine)	2,270	3,517	8.5%	$104,190	$29.62
Paxil® (paroxetine)	1,180	1,701	4.1%	$151,810	$89.25
Effexor® (venlafaxine)	864	1,402	3.4%	$167,024	$119.13
Celexa® (citalopram)	595	942	2.3%	$80,458	$85.41
Luvox® (fluvoxamine)	149	259	0.6%	$26,424	$102.03
TOTALS	*26,755*	*41,281*	*100%*	*$2,461,823*	*$59.63*

Nearly 75% of all the antidepressant claims filled during the months of July and August 2004 were for agents referenced in the aforementioned March 2004 FDA warning letter. The "other" agents included Tricyclic Antidepressants (TCAs) such as amitriptyline, doxepin, and imipramine. A complete list of patients who received these agents is located in Exhibit 1 of this report.

Antipsychotic Drug Use Among Patients Under 18 Years of Age



Antipsychotic Drug Summary Report (July – August 2004)

Drug Class	*Patients*	*Claims*	*Percent of Claims*	*Total Paid*	*Paid per Claim*
Risperdal® (risperidone)	9,269	15,180	41.5%	$2,905,650	$191.41
Seroquel® (quetiapine)	5,042	9,290	25.4%	$1,844,583	$198.56
Abilify® (aripiprazole)	3,270	5,565	15.2%	$1,845,510	$331.63
Zyprexa® (olanzapine)	1,828	3,173	8.7%	$1,048,245	$330.36
Geodon® (ziprasidone)	1,311	2,289	6.3%	$557,256	$243.45
Others (TCAs)	485	760	2.2%	$21,798	$28.68
Symbyax® (olan/fluoxetine)	100	161	0.4%	$40,463	$251.32
Clozaril® (clozapine)	27	129	0.3%	$8,918	$69.14
TOTALS	*21,332*	*36,547*	*100%*	*$8,272,423*	*$226.35*

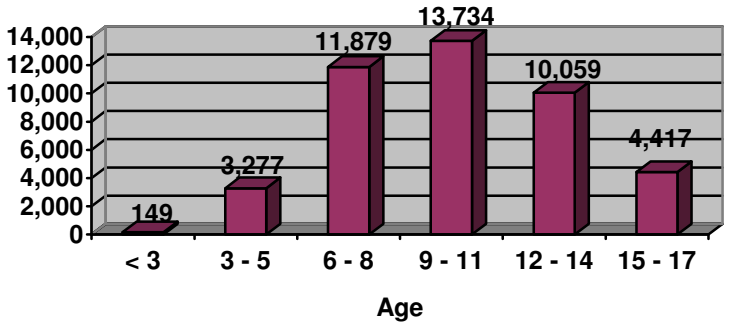
Nearly 98% of all the antipsychotics filled during the months of July and August 2004 for patients under the age of 18 were for atypical antipsychotics. No atypical antipsychotic is FDA-approved to treat patients under the age of 18. A spreadsheet identifying all patients who received antipsychotics is located in Exhibit 1.

III. Demographics

1. Stimulants

From July through August 2004, **43,521** recipients received at least one claim for a stimulant drug. An analysis of the age demographics is shown below. Stimulants should not be used in patients under the age of 3. It appears that 149 recipients under three years of age are currently receiving treatment with a stimulant. A drug class summary report for all drugs included in the study is available in Exhibit 2.

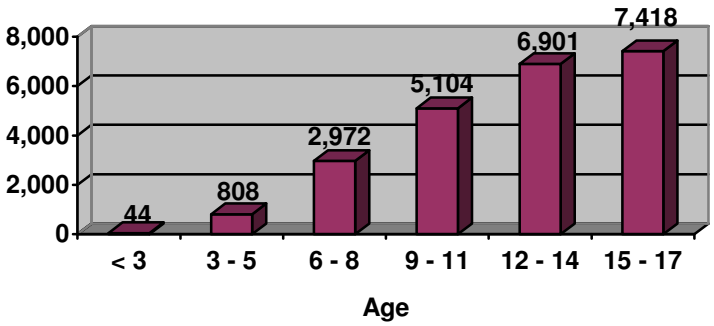
Age Distribution for Stimulant Utilization



2. Antidepressants

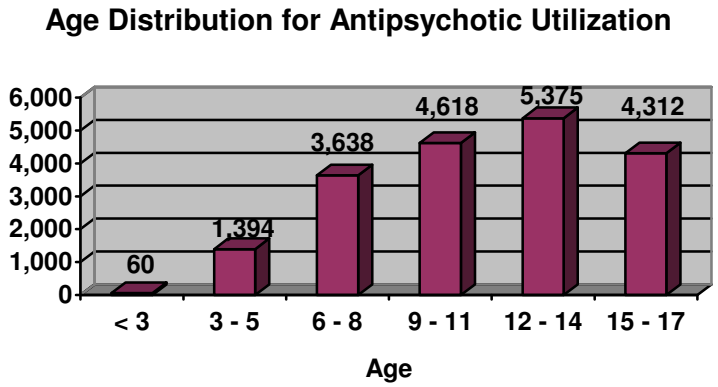
From July through August 2004, **23,183** recipients received at least one claim for an antidepressant. An analysis of the age demographics is presented below. As mentioned earlier, antidepressants should be used with caution in children and adolescents.

Age Distribution for Antidepressant Utilization



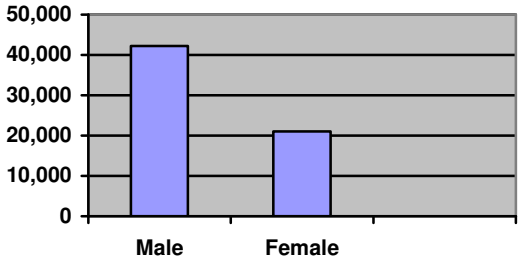
3. Antipsychotics

From July through August 2004, **19,403** recipients received at least one claim for an antipsychotic. An analysis of the age demographics is displayed below.



4. Gender Distribution

The analysis identified 63,118 recipients under the age of 18 who received at least one drug from the three drug classes reviewed. Of these, 42,220 (67%) were male and 20,898 (33%) were female.



IV. Clinical Evaluations

1. Combination Therapy

An analysis of concomitant drug therapy revealed that 19,365 or 31% of patients selected are currently taking more than one of the targeted drug classes simultaneously. Of these, nearly 25% or 4,704 patients are under the age of 9. A complete list of patients and providers who received or prescribed combination therapy is presented as Exhibit 3.

2. Inappropriate Use

Stimulants

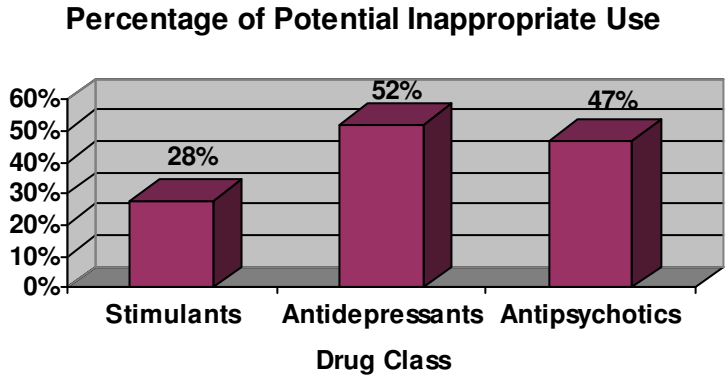
Stimulant use in children is generally limited for the treatment of Attention Deficit Disorder (ADD) or Attention Deficit Hyperactivity Disorder (ADHD). The use of these agents in Narcolepsy is also well documented and established. Of the 43,521 children currently receiving treatment with stimulants, 12,335 or 28% do not have a proper diagnosis to warrant their use.

Antidepressants

As referenced in the introduction section of this report, antidepressant use in children is accompanied with risk of adverse drug events. Only Prozac® (fluoxetine) is FDA-approved for use in children with major depressive disorder. However, currently there appears to be 12,168 patients under 18 who do not have a documented diagnosis for the use of antidepressants. This figure is approximately 52% of all patients analyzed that are currently receiving antidepressants.

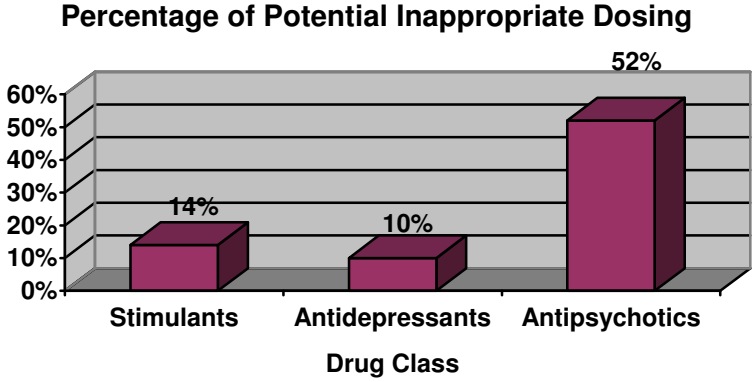
Antipsychotics

As documented earlier, atypical antipsychotics do not have an FDA-approved indication for the use in patients under the age of 18. However, an analysis was performed evaluating the use of these agents among patients without a history of an appropriate diagnosis documented over the past two years. The query revealed that 9,115 patients or 47% of children under 18 years of age did not have a documented diagnosis that would warrant the use of an atypical antipsychotic. A spreadsheet listing all patients who received potentially inappropriate use of the drug classes mentioned above is provided in Exhibit 4.



3. Inappropriate Dosing

A dosing analysis was performed evaluating inappropriate dosing among various drugs within each of the drug classes. A query was performed targeting patients who received "once-daily" drugs in divided doses. Also, claims exceeding maximum doses were also evaluated. The graph below shows the percentage of patients who received inappropriate doses within each drug class. Antipsychotics appear to be the most inappropriately used agents, particularly atypical agents, which are generally dosed once a day. Slightly over 52% of the patients receiving antipsychotics appear to have received inappropriate doses. A list containing both patients and providers who received or prescribed potential inappropriate doses is located in Exhibit 5.



There is an example of at least one patient who received several claims for potential inappropriate doses. As recent as 7/6/04, this patient received consecutive claims for Adderall XR 20mg #60 tablets for a 30-day supply (two doses per day). This agent is generally dosed once daily and its maximum dose is listed as 30mg per day. This patient exceeded the maximum dose by 10mg. In addition to the potentially

inappropriate stimulant dose, this patient has received for seven consecutive months claims for Zyprexa 10mg #60 for 30-day supply. Zyprexa is also generally dosed as one tablet daily. A 20mg tablet is also available in order to simplify the aforementioned claim.

V. Provider Review

An analysis was also performed to identify the prescribing and dispensing providers of agents within all three drug classes. In addition, the providers that prescribed for inappropriate uses and doses were identified. An attached spreadsheet contains all providers identified within each category. Below is a list of the top prescribers within each drug class. A list of all providers is presented in Exhibit 6 of this report.

Top Five Stimulant Prescribers (July – August 2004)

Prescriber ID	*Prescriber*	*Claims*	*Patients*
J7546	Kudisch, Alejandro	727	536
J0145	Mosqueda, Robert	685	562
H6867	Kanneganti, Ravikumar	657	549
H7500	Samaniego, Hector	565	361
K1492	Kallepalli, Bhupala	560	280

The top two prescribers of stimulants are from McAllen, Texas.

Top Five Antidepressant Prescribers (July – August 2004)

Prescriber ID	*Prescriber*	*Claims*	*Patients*
J7546	Kudisch, Alejandro	539	367
D7911	Bates, Joe	528	242
K6999	Bracken, Jill	520	284
H3342	Sargent, Charles H	468	235
C6159	Sargent, Charles A	461	97

The top prescriber of antidepressants also prescribed the highest quantity of stimulant claims.

Top Five Antipsychotic Prescribers (July – August 2004)

Prescriber ID	*Prescriber*	*Claims*	*Patients*
K6992	Bracken, Jill	764	352
F3588	Ravichandran, GK	728	432
D7911	Bates, Joe	601	296
H4832	Iglehart, Sharon	511	214
H6867	Kanneganti, Ravikumar	470	389

V. Summary

Psychotropic drug use among children has a long history of controversy. Clear benefits of these agents have been debated and continue to cause much concern. Nevertheless, abrupt discontinuation and withdrawal of these agents carries enormous risk. Also, countless examples of successful pharmacological treatment of children with psychotropic agents have also been documented. Prudent use of these agents among these patients should be followed along with monitoring for signs or symptoms of adverse drug events.

VI. Appendix

Exhibit 1- **Patient List**
Exhibit 2- **Drug Class Summary Report**
Exhibit 3- **Combination Therapy Summary**
Exhibit 4- **No Diagnosis – Patient Summary**
Exhibit 5- **Patient and Provider Dosing Analysis**
Exhibit 6- **Provider Summary**