

Risperdal Pediatric Market Opportunity

August, 2000

EXHIBIT
P-18
Date: _____
M.L. GRAY, CSR, RPR

**PLAINTIFF'S
EXHIBIT
18**



Agenda

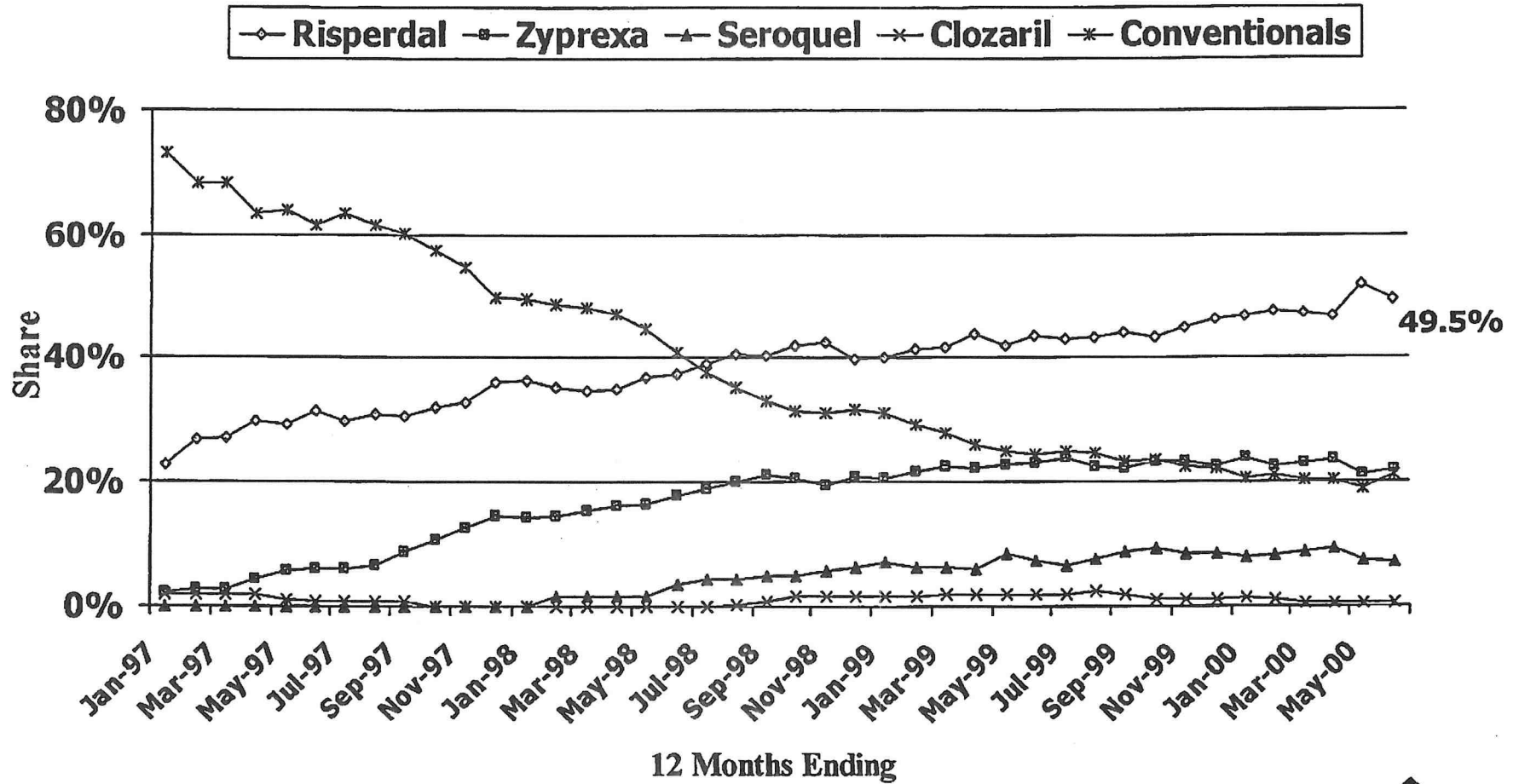
- Secondary data review
 - antipsychotic use in pediatric market
 - child psychiatrists opportunity
 - sales force targeting
 - dollar potential
- Risperdal qualitative pediatric market research
 - use of atypical antipsychotics in children
 - reaction to Risperdal pediatric data

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Antipsychotic Share in Pediatrics

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Source: IMS Health, NDTI

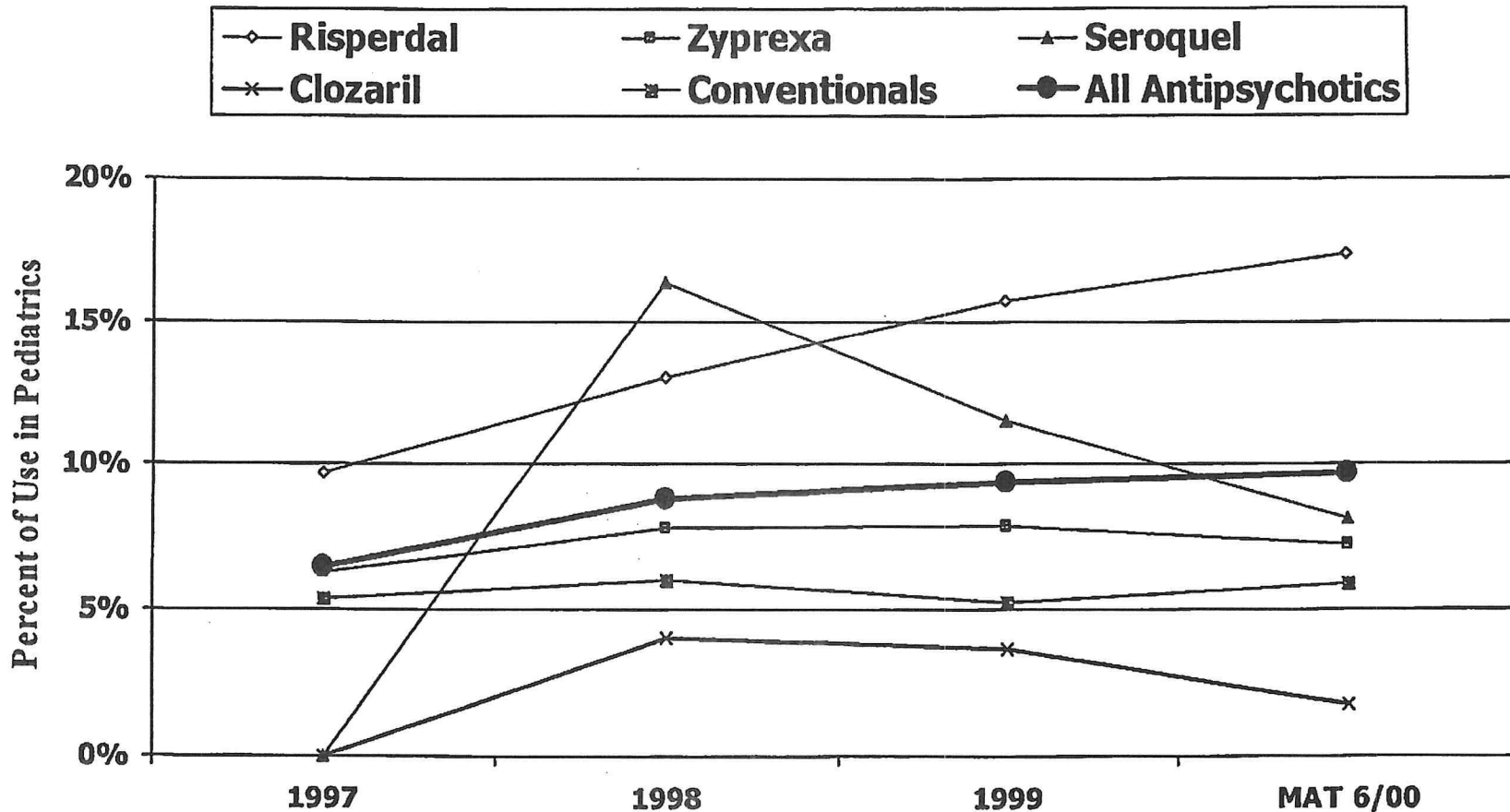
Pediatrics defined as ages 0-19.

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Antipsychotics' Percent of Overall Drug Use in Pediatrics

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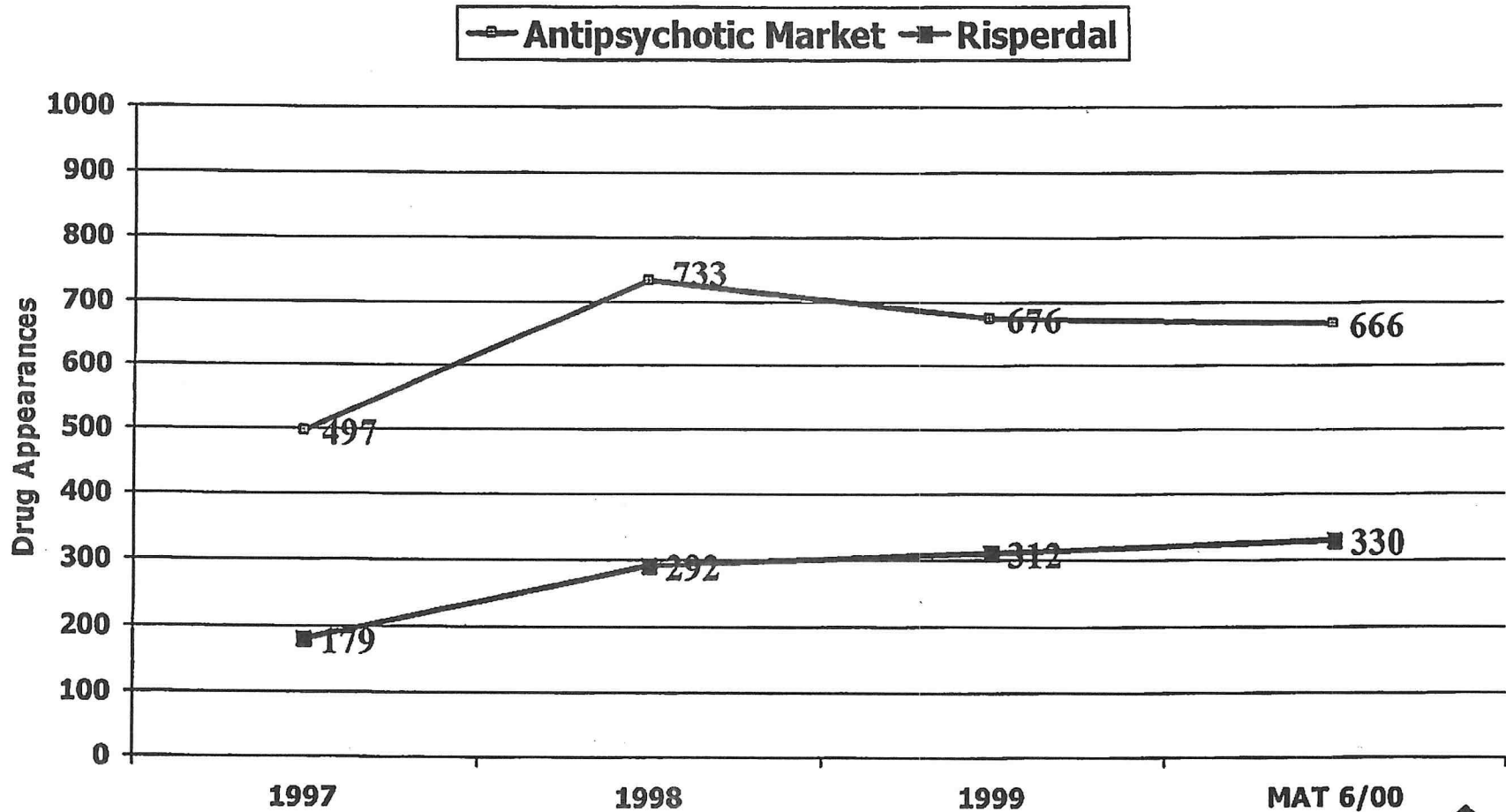
Source: IMS Health, NDTI

Pediatrics defined as ages 0-19.

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Antipsychotic Market: Pediatric Volume



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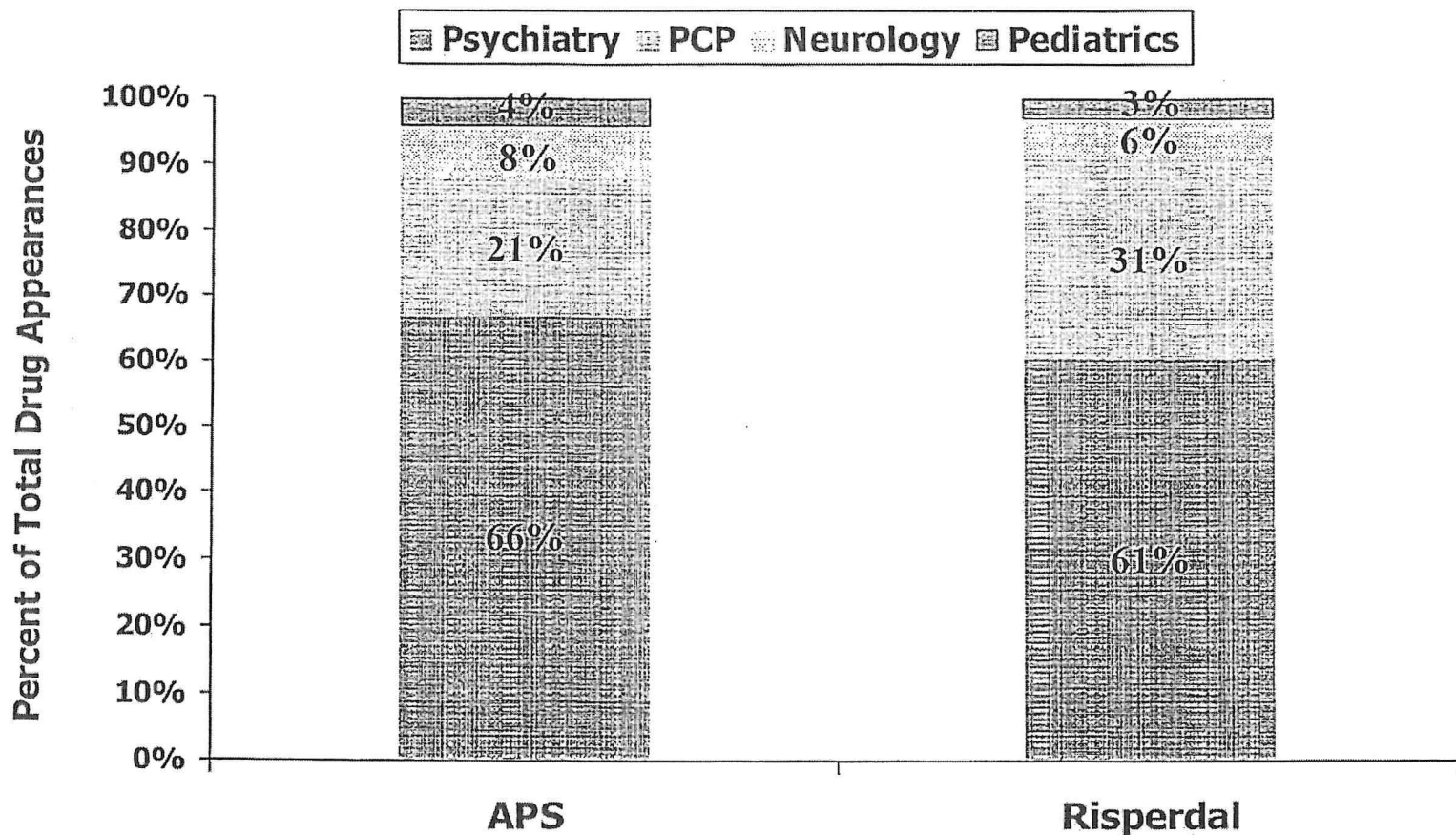


Source: IMS Health, NDTI

Pediatrics defined as ages 0-19.

Pediatric Antipsychotic Use by Specialty

- Psychiatrists are the top prescribers of antipsychotics in pediatric patients



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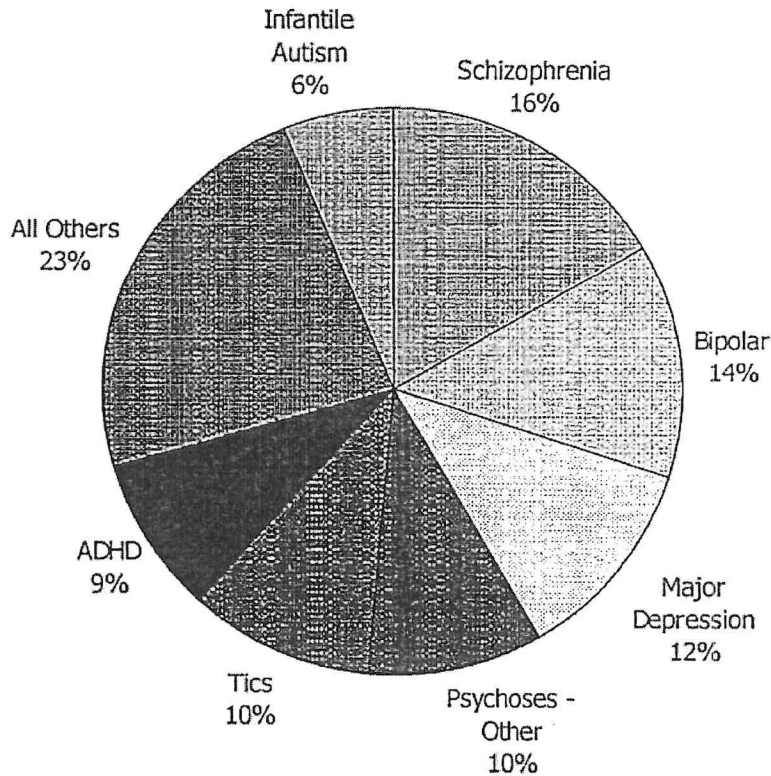
Source: IMS Health, NDTI, MAT 6/00

Pediatrics defined as ages 0-19.

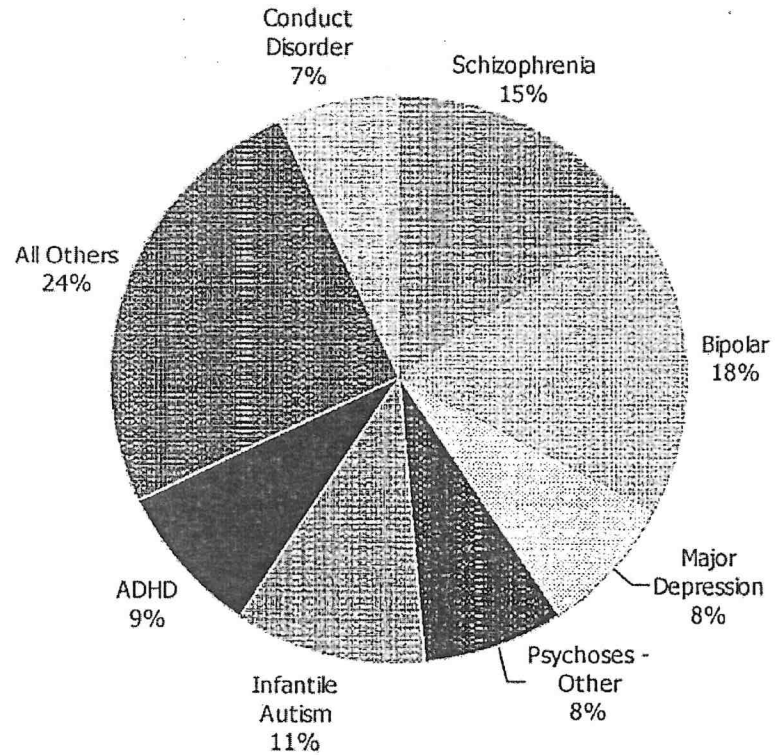
Leading Diagnoses Treated in Pediatrics With Antipsychotics

- Schizophrenia and bipolar disorder are the most common diagnoses treated by antipsychotics in the pediatric population*

APS Market



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Source: IMS Health, NDTI, MAT 6/00

Pediatrics defined as ages 0-19.

Market Analysis

Child Psychiatry Opportunity

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- Number child psychiatrists 5,207
- Cross Matched to APS Decile 5-9 (48.9%) 2,544
- Cross Matched to APS Decile 8-9 (14.3%) 745
- Total APS Sales (May '99 - Apr '00) \$196 MM

Product	\$ Sales	NRx Share
Risperdal	\$85 Million	44.5%
Zyprexa	\$48 Million	23.6%
Seroquel	\$21 Million	11.0%
Conventionals	\$49 Million	18.7%

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Risperdal Pediatric Market Research Objective / Methodology

- To understand how psychiatrists use atypical antipsychotics in children and adolescents, and the impact of Risperdal clinical data in children with conduct disorder.
 - explore current use of atypicals, including diagnoses, patient types/age, perceived differences in agents, and agent preference
 - review/refine the messages included in the Risperdal pediatric data monograph.
- Interviews with child and general psychiatrists
 - Phase I: 30 telephone interviews (n=15 child, 15 general)
 - Phase II: 30 in-person interviews (n= 13 child, 17 general)
 - Respondents were screened to meet specific pediatric criteria
 - Interviews were completed in March and April, 2000

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Diagnoses that Require Treatment with Antipsychotics

age 3 to 6 47% use APS (n=28)	age 7 to 12 78% use APS (n=47)	age 13 to 19 98% use APS (n=59)
<ul style="list-style-type: none"> • pervasive developmental disorder (PDD) / autism (54%) • bipolar disorder (BPD) (46%) • psychoses NOS (46%) • severe ADD (32%) • Tourette's syndrome (21%) • conduct disorder (18%) • agitation / aggression (18%) • schizophrenia (18%) • intermittent explosive disorder (14%) 	<ul style="list-style-type: none"> • BPD (70%) • psychoses NOS (49%) • severe ADD (47%) • schizophrenia (40%) • PDD / autism (28%) • conduct disorder (28%) • Tourette's syndrome (21%) • major depression w/ psychoses (21%) • intermittent explosive disorder (13%) • obsessive-compulsive disorder (13%) 	<ul style="list-style-type: none"> • BPD (83%) • schizophrenia (64%) • psychoses NOS (53%) • major depression w/ psychoses (41%) • severe ADD (29%) • conduct disorder (22%) • PDD / autism (20%) • substance abuse (19%) • OCD (15%) • agitation / aggression (15%) • impulse control disorder (14%)



Difficulty in Diagnosing Pediatric Patients

- Many of these diagnoses, such as ADD, BPD, PTSD, conduct disorder, and substance abuse often coexist in children.
- Both adult and child psychiatrists described a general reluctance to "label" an ADD child (for example) with conduct disorder, BPD, or schizophrenia, despite the realization that characteristic symptoms of each disorder are evident.

"A lot of times you have a history where a kid has been diagnosed as bipolar by one guy, schizophrenic by another guy, and someone else thinks they have ADHD, while the parents do not think anything is wrong. You can look through their records and take your pick [of a diagnosis]. A single, clear diagnosis is the exception to the rule." - general psychiatrist

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Use of Atypical Antipsychotics in Pediatric Patients

- For children with non-psychotic diagnoses, atypicals are most often considered second-, third-, or fourth-line therapy after other classes of medications have failed.
 - *Example:* Children / teenagers with severe ADD or conduct disorder who receive antipsychotics were described as highly aggressive or violent, despite taking: stimulants, alpha antagonists, mood stabilizers
 - In refractory patients, antipsychotics benefit by minimizing aggressiveness and calming the child / adolescent so that he or she can attend school and socialize normally
- Children with schizophrenia represent the exception to this rule, where atypicals are the cornerstone of therapy.

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Use of Atypical Antipsychotics in Pediatric Patients - Barrier to Use

- Lack of FDA approval in pediatric patients
- Lack of clinical data to support atypical agent use in pediatrics / teenagers
- Acute side effects (*ie*, weight gain, lactation)
- Long-term side effects (*ie*, tardive dyskinesia)
- Social stigma associated with antipsychotic use

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Pediatric Population Antipsychotic Preference

- Risperdal is the preferred antipsychotic for children and teens.
- Risperdal and Zyprexa are considered equivalent in terms of antipsychotic efficacy.
 - However, Risperdal and Zyprexa are appropriate initial choices for particular patient circumstances.
- As a relatively new option for children, Seroquel's role in pediatrics is not clear.
 - Several psychiatrists were relatively less impressed with its efficacy.
 - However, side effects (sedation and weight gain) are less common and less severe with Seroquel *vs* Zyprexa and Risperdal.
 - Several lamented the lack of pediatric clinical data

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Pediatric Population Risperdal Advantages

- first available atypical antipsychotic (high comfort level, familiarity)
- smaller tablet strengths and liquid formulation, making it easier to dose/titrate Risperdal in children
- lower tablet potency (1 mg vs 2.5 mg or 10 mg) which some parents and children find appealing / reassuring
- tablets are scored, making them easier to split if necessary
- less weight gain than Zyprexa, making it especially appropriate for use in adolescents
- quick onset of action (*ie*, patient calmed within hours to days), which is unique to Risperdal
- no specific concern about diabetes (unlike Zyprexa), making it an appropriate choice in children with diagnosis or history of diabetes
- less sedating than Zyprexa, making it useful for some children, especially those who need doses while in school

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Pediatric Population Risperdal Disadvantages

- more likely to cause extrapyramidal symptoms (EPS), including tremor and stiffness
- higher long-term risk of tardive dyskinesia (TD)
- more likely to cause increased prolactin levels, gynecomastia, lactation
- causes significant weight gain (which can be advantageous in children with ADD who are often too thin)

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Rationale for Atypical Antipsychotics in Non-Psychotic Diagnoses

Risperdal preferred by 69% of psychiatrists who discussed non-psychotic diagnoses	Zyprexa preferred by 23% of psychiatrists who discussed non-psychotic diagnoses	Seroquel preferred by 8% of psychiatrists who discussed non-psychotic diagnoses
<ul style="list-style-type: none"> • less weight gain compared with Zyprexa • more familiar / more experience with Risperdal • anti-anxiety properties • mood stabilizing properties • easy to dose • liquid formulation • well tolerated • well tolerated at low doses • faster onset of action • less risk of diabetes • more data in children • less sedating than Zyprexa 	<ul style="list-style-type: none"> • less EPS compared with Risperdal • calms children more effectively than Risperdal • more sedating than Risperdal (can be valuable if not sleeping) • weight gain (valuable in some patients) • more experience with Zyprexa • well tolerated 	<ul style="list-style-type: none"> • calming without too much sedation • safer than Risperdal and Zyprexa for non-psychotic diagnoses • effective in non-psychotic diagnoses

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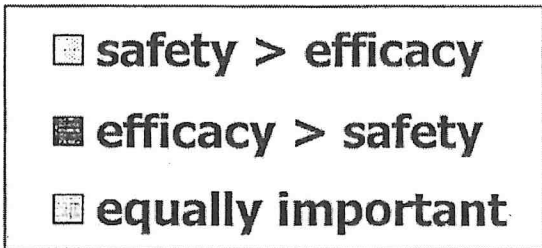
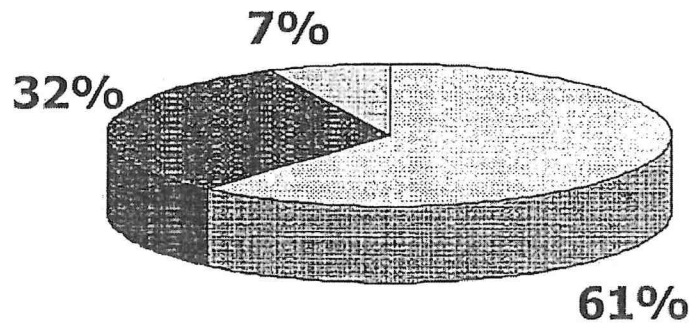
Risperdal Data Review

- Physicians were exposed to a monograph of Risperdal pediatric data which included:
 - Results of a placebo controlled double-blind study (n=20) evaluating Risperdal for the outpatient treatment of severe conduct disorder in children
 - Results of a placebo controlled double-blind study (n=118) evaluating Risperdal for the outpatient treatment of severe conduct problems in children with mental retardation
 - An overview of Risperdal use in the pediatric population

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Relative Importance of Safety and Efficacy Data to Psychs when Reviewing Pediatric Clinical Trial Results



- Prior to reading the draft Risperdal monograph, psych-iatrists were asked whether they are relatively more attentive to safety or efficacy data when reviewing results of clinical trials in children:
 - **61% said safety is relatively more important than efficacy.** These respondents were more likely to be child psychs.
 - **32% said efficacy is relatively more important than safety.** These respondents were more likely to be general psychs.



Risperdal Data Review

Overall Message

- Generally, the monograph effectively communicated the availability of clinical evidence to support the efficacy and safety of Risperdal in children with conduct disorder.
 - "Risperdal is safe and effective in conduct disorder, regardless of whether the patient is mentally retarded."
 - "Risperdal is good for conduct disorder in children and adolescents."
 - "Risperdal is an effective and convenient agent to use in conduct disorder with a low risk of toxicities."
 - "Risperdal has been tested in younger children and shown to be effective."
 - "Risperdal works; we are on the right track."
 - "Risperdal can control conduct disorder at low doses."

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Risperdal Data Review

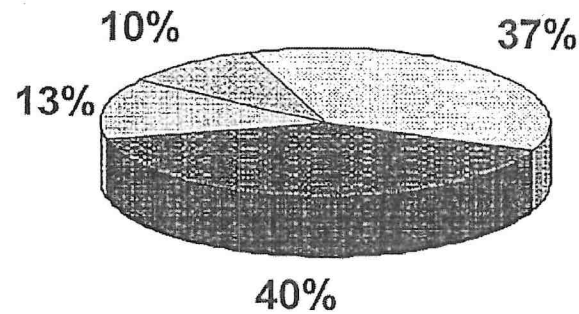
Reaction to Message

- Half the respondents agreed with main Risperdal message based on their own positive experience using antipsychotics in children conduct disorder or similar conditions.
 - These respondents were enthusiastic about the availability of clinical data to support their current treatment approach, often characterizing it as "reassuring."
- The other half was relatively suspicious of the findings.
 - Some characterized the data as difficult to interpret, in part because "conduct disorder" is not straightforward. Conduct disorder often overlaps with BPD and other conditions. They need details on patient selection criteria and concurrent diagnoses
 - Others contested the basic premise of the clinical trials, using atypicals to treat conduct disorder
 - Others indicated that the results do not compare with their experience.



Overall Impact of Risperdal Data

- Psychiatrists consistently reported that they have not seen pediatric data for Zyprexa or Seroquel, making the availability of such data for Risperdal a differentiator.



- change - will increase use
- no change - already convinced of value
- no change - need more information
- no change - not convinced of value

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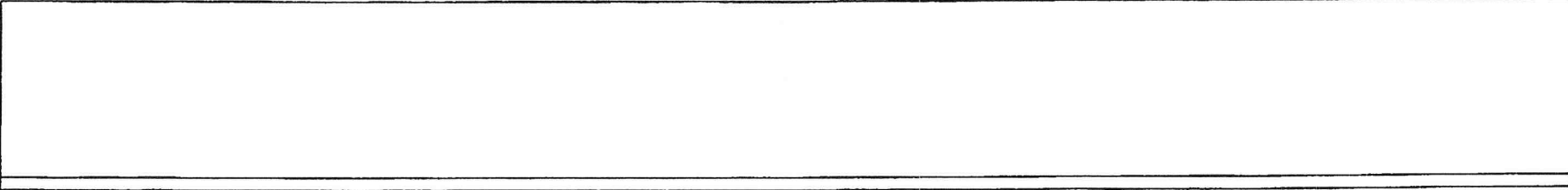


Conclusions

- Pediatric patients represent a large and growing market opportunity for Risperdal.
- Antipsychotics are used in a variety of pediatric conditions
 - first-line in schizophrenia
 - refractory use in non-psychotic disorders for aggression & agitation
- Risperdal holds a leadership position over other atypical antipsychotics
 - Most respondents use Risperdal preferentially in pediatric patients.
 - Prolactinemia and long-term adverse event concerns appear to be the most significant barriers to more widespread Risperdal use in children / teenagers.
- Data in conduct disorder are valuable for some, but others need more study details to ensure effective communication of Risperdal message.
- Additional data is desired by psychiatrists
 - long-term safety data

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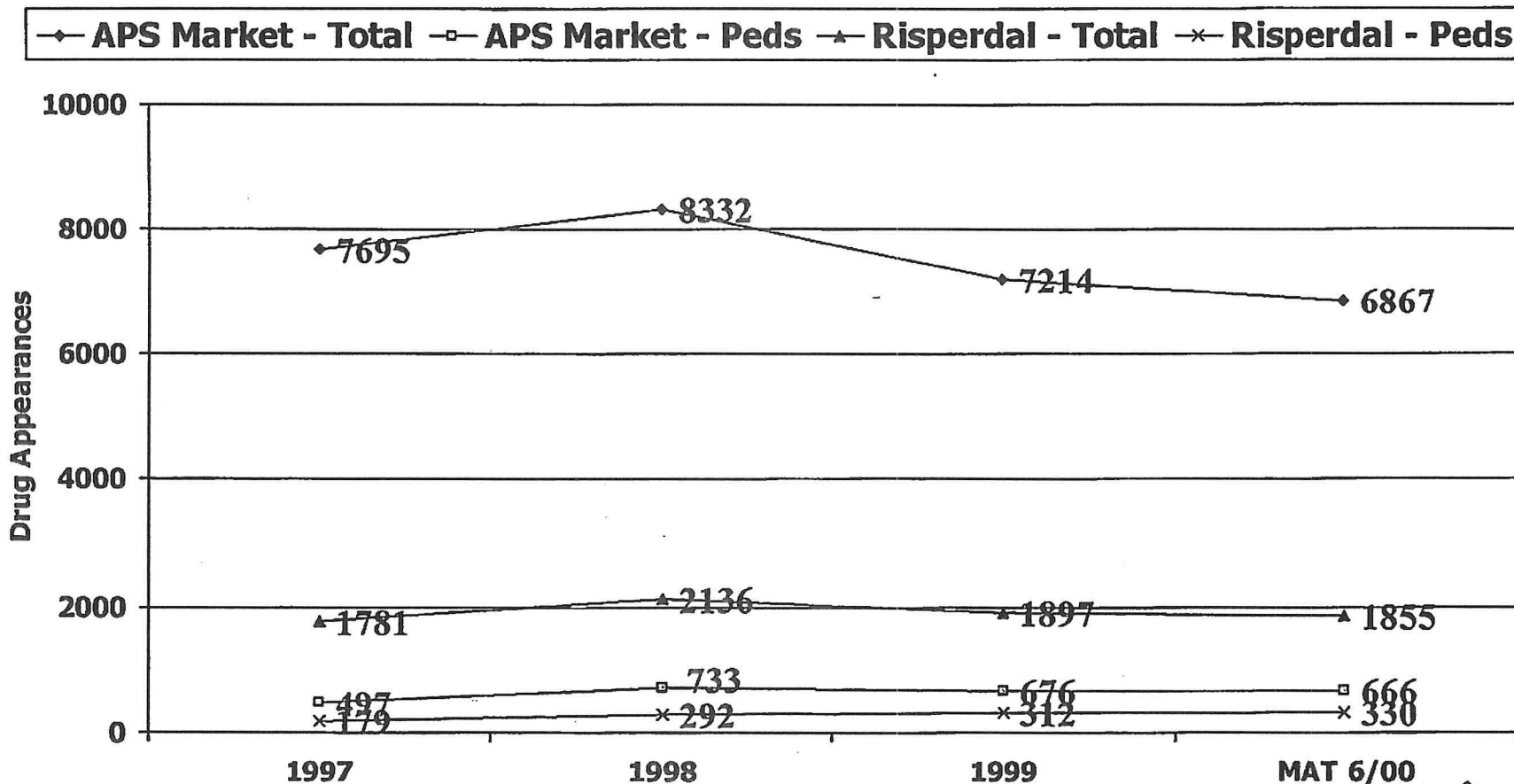




Backup Slides

Antipsychotic Market: Pediatric Versus Adult Volume Of Use

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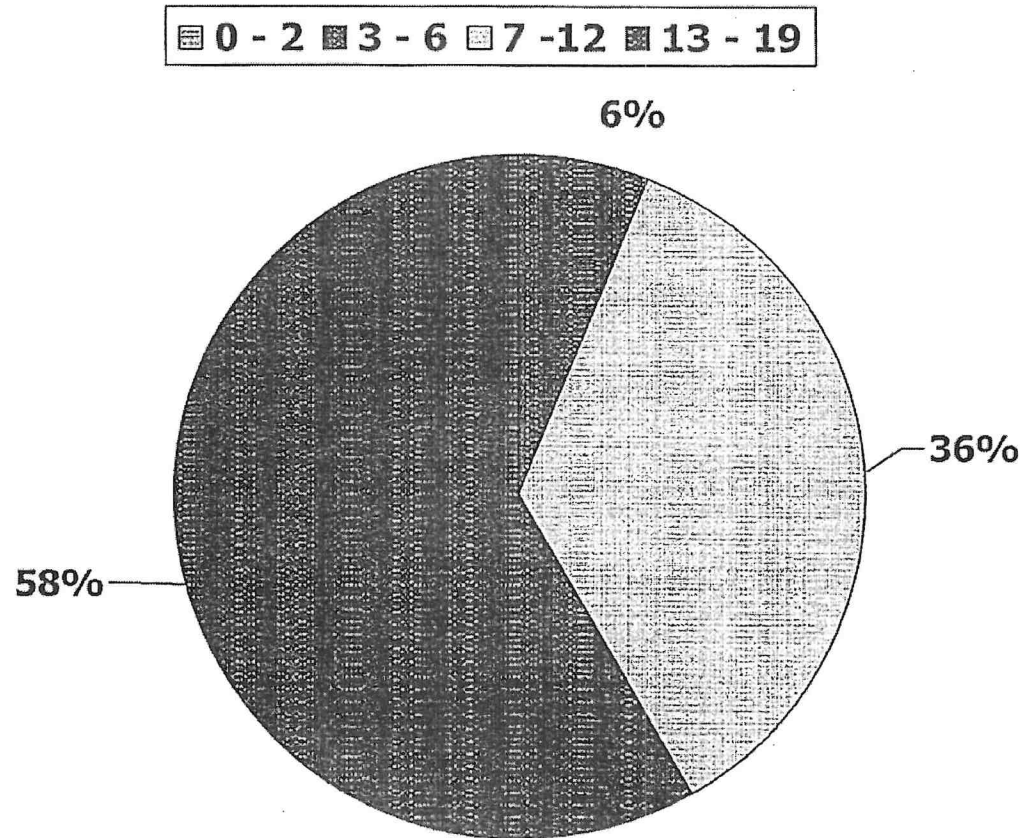
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Source: IMS Health, NDTI

Pediatrics defined as ages 0-19.

Antipsychotic Pediatric Use By Age



Source: IMS Health, NDTI, MAT 6/00

Pediatrics defined as ages 0-19.

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Risperdal Pediatric Market Research Methodology

- Interviews with child and general psychiatrists
 - Phase I: 30 telephone interviews (n=15 child, 15 general)
 - Phase II: 30 in-person interviews (n= 13 child, 17 general)
 - Respondents were screened to meet specific criteria, including:
 - more than 20% of patient population is younger than age 19
 - *child psychiatrists*: 25 atypical Rx in the past month for children
 - *general psychiatrists*: 8 atypical Rx in the past month for children
- Interviews were completed in March and April, 2000

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