PROTOCOL: An Open Label Trial of Aripiprazole in the Treatment of Conduct Disorder in Adolescents.

Rationale:

The use of atypical antipsychotics in children began in 1992 with several small case series with clozapine. Since that time, five other atypical agents, risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole have been introduced into the US market. The newer atypical agents are not associated with agranulocytosis that has limited the usefulness of clozapine. Among the atypical antipsychotics, risperidone has remained the most extensively studied in children and adolescents, for a variety of problems, including Tourette's disorder, conduct disorder, schizophrenia, aggression, and pervasive development disorder. Risperidone has been shown to be an effective treatment in many of these disorders. However, weight gain, hyperprolactinemia, and extrapyramidal symptoms (EPS) are troublesome adverse effects more commonly associated with risperidone such that the drug's utility in this aged patient population is limited. We expect that the utility of aripiprazole in treating the pediatric population will not be limited by adverse effects like the other atypical antipsychotics.

Previous Work:

Several small studies have found risperidone to be more effective than placebo in treating children and adolescents with either aggression or conduct disorder. In a 10-week, randomized, double-blind study (n=20), risperidone was superior to placebo in reducing most measures of the Rating of Aggression Against People and/or Property Scale (RAAPP), when dosed at an average of 0.028mg/kg/day [range = 0.75-1.50 mg/day] (Findling et al 2000). The data also suggested that treatment with risperidone was associated with weight gain. The predicted weight gain from a repeated measures analysis for the risperidone group of 4.2±0.7kg was greater than the placebo group ($p=0.003$). There was no difference in the incidence of EPS at endpoint according the Simpson-Angus EPS (SAEPS) rating scale.

Buitelaar et al (2001) assessed the efficacy of risperidone in the treatment of aggression. Thirty-eight adolescents were randomized to either risperidone or placebo in a double-blind fashion. The mean daily dose of risperidone at end of treatment (6 weeks) was 2.9mg [range = 1.5-4 mg]. Risperidone treatment produced improvement on the Clinical Global Impression-Severity (CGI-S) scale (LOCF, $p<0.001$) and the at-school Aberrant Behavior Checklist (ABC) overall and hyperactivity scales ($p<0.05$). In the risperidone group, following a 2-week washout following the 6-week trial worsening on all efficacy measures (CGI-S, Overt Aggression Scale-Modified (OAS-M), and the ABC. Weight gain was significant in the risperidone group (3.5% body weight increase, range –1 to +6kg, $p<0.05$). Transient tiredness was also noted in 58% of drug-treated subjects, and was also the reason for dose reduction in five of the drug-treated subjects. Extrapyramidal Side Effect Rating Scale (ESRS) scores increased for Parkinsonism (cluster II) at endpoint compared to placebo ($p<0.05$).

Bellinghen et al (2001) compared risperidone (n=6) to placebo (n=7) in the treatment of behavioral disturbances in children and adolescents. Thirteen patients were enrolled in a 4-week double-blind, placebo-controlled study. Risperidone (mean dose = 0.05mg/kg; mean total dose = 1.2 mg/day) was more effective than placebo in improving ABC cluster scores for irritation and hyperactivity, the CGI scale. No significant differences in EPS symptoms or weight gain were seen between the treatment groups. The lack of any adverse effect differences is not surprising considering the low dose of risperidone and the small number of patients enrolled in the study.

Methods:

Dose and Schedule of Treatment: The proposed study will be a 6-week open label study evaluating aripiprazole in the treatment of 12 male post-pubertal adolescents (13-17 years, Tanner Stage 4) diagnosed with conduct disorder. The initial dose depending on the weight of the patient will be as follows: < 25 kg = 1 mg/d; 25-50 kg = 2 mg/d; 50-70 kg = 5 mg/d; > 70 kg = 10 mg/d (Data on File, 2003, Bristol-Myers Squibb). Thereafter the dose will be flexible based on response and tolerance.

Main outcome measures: The primary outcome efficacy measures will be the Rating of Aggression Against People and/or Property Scale (RAAPP) (Kemph et al 1993), Overt Aggression Scale-Modified (OAS-M) (Kay et al 1988), and Children's Aggression Scale-Parent Version (CAS-P) (Halpern et al 2002) while the secondary outcome measure will be the CGI severity and improvement scale (NIMH, 1985a). Safety measures for extrapyramidal adverse effects will include the AIMS (NIMH, 1985b) for tardive dyskinesia, Barnes Akathisia Scale (Barnes 1989) (BAS) and the Simpson-Angus Scale (SAS) (Simpson and Angus 1970). The UKU (Lingjaerde et al 1987) will be used for monitoring non-motor adverse effects. Height, weight and body mass index measurements as well as initial and endpoint fasting blood sugars and lipids will assess the effect of weight change. Obtaining serum prolactin levels as well as screening for the sexual dysfunction adverse effects including galactorrhea, gynecomastia, menstrual irregularities and changes in libido will assess sexual dysfunction adverse effects. An initial and endpoint ECG will be obtained to monitor patients for any changes in the QT-corrected interval. A gamma-GT will be collected to monitor liver function.

Schedule of Events:

Procedure	**screening** (-7 to –28days)	**baseline**	**week 1**	**week 2**	**week 4**	**week 6**
History-Demographics	X					
Physical Exam	X					X
ECG	X					X
Vitals, Height, Weight, BMI	X	X	X	X	X	X
Urine Collection	X					X
Phlebotomy	X					X
Dispense Study Drug		X	X	X	X	X
Determine medication compliance			X	X	X	X

Laboratory Tests

fasting glucose	X					X
fasting lipid profile:						
total cholesterol	X					X
HDL-cholesterol	X					X
LDL-cholesterol	X					X
Triglicerides	X					X
Prolactin	X					X
Gamma GT	X					X
CBC	X					X
Urine Drugs of Abuse Screen	X					X

Psychiatric Rating Scales

RAAPP	X	X	X	X	X
CAS-P	X	X	X	X	X
OAS	X	X	X	X	X
CGI-S	X	X	X	X	X
CGI-I		X	X	X	X

Side Effect Rating Scales

AIMS	X	X	X	X	X
SAS	X	X	X	X	X
UKU	X	X	X	X	X
BAS	X	X	X	X	X

References:

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Budget: Open label Aripiprazole-Conduct Disorder study

Procedure	**Screening**	**Baseline**	**Week 1**	**Week 2**	**Week 4**	**Week 6**
History-Demographics	50.00					
Physical Exam	100.00					100.00
ECG	125.00					125.00
Vitals, Height, Weight, BMI	10.00	10.00	10.00	10.00	10.00	10.00
Urine Collection	5.00					5.00
Phlebotomy	10.00					10.00
Laboratory Tests						
Fasting glucose	12.00					12.00
Fasting lipid profile:						
Total cholesterol	15.00					15.00
HDL-cholesterol	29.00					29.00
LDL-cholesterol	0.00					0.00
Triglycerides	19.00					19.00
Prolactin	53.00					53.00
Gamma GT	21.00					21.00
CBC	27.00					27.00
Urine Drugs of Abuse Screen	85.00					85.00
Psychiatric Rating Scales						
RAAPP		25.00	25.00	25.00	25.00	25.00
CAS-P		25.00	25.00	25.00	25.00	25.00
OAS		25.00	25.00	25.00	25.00	25.00
CGI-S		25.00	25.00	25.00	25.00	25.00
CGI-I		25.00	25.00	25.00	25.00	25.00
Side Effect Rating Scales						
AIMS/BAS/SAS		25.00	25.00	25.00	25.00	25.00
UKU		25.00	25.00	25.00	25.00	25.00
Investigator Fee	100.00	100.00	100.00	100.00	100.00	100.00
Study Coordinator Fee	50.00	50.00	50.00	50.00	50.00	50.00
Subject Compensation	25.00	25.00	25.00	25.00	25.00	25.00

Total direct costs per visit	886.00	360.00	360.00	360.00	360.00	861.00
Total direct costs per completed subject						3187.00
Total indirect costs per visit (25%)	184.00	90.00	90.00	90.00	90.00	215.25
Total indirect costs per completed subject						759.25
Total costs per completed subject						**3796.25**