

Research Article

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Comparing Efficacy and Safety of Aripiprazole to Placebo in Children and Adolescents with Tourette's Syndrome

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Abstract

Objective: Primary: To compare the efficacy of aripiprazole to placebo in the suppression of tics in children and adolescents (7-17) with a diagnosis of Tourette's in one of 33 sites. Secondary: To evaluate the safety and tolerability of Aripiprazole once daily in children and adolescents.

Method: After signing an ICF/IAF Four subjects were screened at our site, three of which were children, and one adolescent. Subjects were randomized to either a low dose, high dose, or placebo, 1:1:1 according to their weight (low dose for those at or less than 50 kg, high dose for those over 50 kg). Aripiprazole 5-10 mg for low dose and 10-20 mg for high dose. Subjects were seen at the clinic at weeks 1, 2, 4, 6 and 8. A telephone contact was made to the subjects on weeks 3, 5 and 7. Primary efficacy measure was change from baseline to end of study (week 8) in Total Tic Score (TTS) of the Yale Global Tic Severity Scale (YGTSS). Secondary measure was to evaluate the safety and tolerability of aripiprazole in participants.

Introduction

Gilles de la Tourette Syndrome (TS) is a neuropsychiatric condition characterized by a rapid, sudden recurrent, non-rhythmic, stereotyped motor movements and vocalizations (tics). These can be simple or complex in nature. They start in early childhood and are most prominent around 10 years of age. The tics wax and wane through their course and decrease by late adolescence and adulthood. The tics are typically chronic and have to last for one year or more [1] and cause psychological impairment [1,2]. The disorder is thought to often be accompanied by comorbid OCD (50%) and/or ADHD (50%) [2,3]. The prevalence ranges from 0.3-1.0% [2,3]. It has a strong heritable component, possibly polygenic [3] and possibly in an autosomal dominant pattern [4,5]. It is believed to be due to a disturbance in the dopaminergic and serotonergic systems [6,3] although other systems may be involved like noradrenergic, glutamatergic, GABA-ergic, cholinergic, and opioid systems [5,7]. The implicated areas of the brain where dopaminergic and serotonergic pathways interact are believed to be basal ganglia (the striatum) and the prefrontal cortex. The thalamus may also be implicated [3,6]. MRI studies and electrophysiological investigations have identified alterations in brain areas of the cortico-striato-thalamic cortical circuits. Studies using amphetamine challenge to study D2 receptors

availability in striatal circuits have revealed increased dopamine release in ventral striated areas in TS patients after amphetamine challenge [2].

1. Abbreviations

| | |
|---------|--|
| AIMS | : Abnormal Involuntary Movement Scale |
| BARS | : Barnes Akathisia Rating Scale |
| CDRS-R | : Children's Depression Rating Scale-Revised |
| CGII | : Clinical Global Impression Scale Improvement |
| CGIS | : Clinician Global Impression Scale |
| C SSRS | : Columbia Suicide Severity Rating Scale |
| CY BOCS | : Children's Yale-Brown Obsessive Compulsive Scale |
| PARS | : Pediatric Anxiety Rating Scale |
| SAS | : Simpson Angus Scale |
| SNAP | : Swanson, Nolan and Pelham Rating Scale for ADHD |
| TS | : Tourette syndrome |

| | | |
|-------|---|--------------------------------|
| TTS | : | Total Tic Score |
| YGTSS | : | Yale Global Tic Severity Scale |

Treatment

Treatment of TS can be subdivided into non-pharmacological and pharmacological.

Non-pharmacological

1. Behavioral treatment most successful is Habit Reversal Training (HRT) [8].
2. Deep Brain Stimulation in refractory TS [9,10].

Pharmacological

1. Positive effects for D2 dopamine receptor blockage have been reported in the treatment of tics for 40 years, although actual evidence based on RCT are limited [6,11].
2. Most commonly used medications:
 - a. Typical Antipsychotic Agents
 - i. Haloperidol
 - ii. Pimozide
 - b. Atypical Antipsychotics:
 - i. Aripiprazole
 - ii. Olanzapine
 - iii. Quetiapine
 - iv. Risperidone
 - v. Ziprasidone
 - c. Alpha-adrenergic agonists
 - i. Clonidine
 - ii. Guanfacine
 - d. Benzamides
 - i. Sulpiride
 - ii. Tiapride

Aripiprazole showed promising results in open-label studies because it has high affinity to D2 receptors but acts as a partial agonist to D2, 5HT1A and antagonistic of 5HT2A, however, there has not been any RTC with sizable populations to demonstrate the efficacy and safety of Aripiprazole in treating Tourette's Syndrome in children and adolescents until now [12-16].

Design

This report shows the results of our site (4 subjects). 33 sites

were involved in the large study (110 subjects). 110 subjects in two weight groups (low groups and high groups). The subjects were divided into three groups: 1/3rd of subjects in the low group, receiving 5-10mg of aripiprazole, 1/3rd of subjects in the high group receiving 10-20 mg of aripiprazole, and 1/3rd of subjects were randomized to placebo. The IRB used was Quorum Review INC.

2 Phases

- 1) Pre-treatment phase: screening and washout period.
- 2) Treatment phase: 8 weeks with baseline visit (day 0).

All psychotropic medications were discontinued for at least 14 days prior to baseline. Psychostimulant medication was permitted during the trial provided the dose was stable for four weeks prior to the screening visit, and the subjects did not develop or have an exacerbation of tics. All SSRI and SNRI medications were discontinued 28 days prior to baseline.

Assessments

After signing an ICF/IAF, subjects were screened using DSM-IV-TR criteria for a diagnosis of Tourette's syndrome by the Principal Investigator. K-SADS-PL- with diagnostic supplements was administered to confirm diagnosis by the Principal Investigator. After washout of prohibited medications according to the protocol, the following instruments were administered at screening:

1. YGTSS: TSS (of more than or equal to 20 at screening and baseline).
2. CYBOCS was completed.
3. CSSRS was completed.
4. Body weight, vital signs with blood pressure and heart rate were measured (subject supine for 5 minutes and standing for 2 minutes.).
5. 12 lead ECG was performed.
6. Fasting blood samples collected.
7. Urinalysis collected.
8. Urine drug screen administered.
9. Blood samples obtained for a serum pregnancy test.
10. Thyroid function test was performed.
11. Prolactin levels were performed.
12. Clinical laboratory tests were performed.

At Baseline

YGTSS, CGI-TS, SNAP-IV, CYBOCS, CDRS-R, PARS, and C-SSRS (since last visit), SAS, AIMS and BARS. Vital

signs and height, body weight and waist circumference, physical examination, 3-12 lead ECG were all performed. Urine for drug screen was collected. Subjects were dispensed study drug. Adverse Events and concomitant medications were recorded.

Treatment

Subjects continued IP through week 7 taking the last dose of the IP one day before week 8. Subjects were seen at the clinic at weeks 1, 2, 4 and 6. The following instruments were administered, YGTSS, CGI-TS, SNAP-IV, CY-BOCS, C-SSRS, SAS, AIMS and BARS. CDRS-R and PARS were only performed at weeks 2 and 4. Weeks 3, 5 and 7 were telephonic contacts only. At week 4 all procedures including CDRS-R and PARS, 12 lead ECG, complete physical examination, height, weight, waist circumference, vital signs, fasting blood samples, urinalysis and pharmacokinetics were performed.

Results

There were four subjects that completed the study; 1 male adolescent (13 years) and 3 children; 2 females ages 8 and 9, and one male age 7. None of the subjects had OCD symptoms.

YGTSS: Scores ranged from 44-79 at baseline, and from 0-23 at completion (week 8). In subject 3175, baseline was 44 compared to completion of 10. In subject 3085 baseline was 63 compared to a completion score of 23. In subject 3071 baseline was 79 compared to a completion of 14. Lastly, subject 3012's scores fell from 75 at baseline to 0.5 at completion.

CDRS-R: Scores ranged from 18-32 at baseline and from 17-19 at completion (week 8). In subject 3175, baseline vs completion was 32:17. For subject 3085, baseline vs completion was 19:17. For subject 3071 baseline vs completion was 27:17. Finally, subject 3012 was 18 at baseline compared to 19 at completion.

CGI-S: Score of 4 at baseline and scores of 1-2 at completion (week 8). In subject 3175 baseline compared to completion was 4:2. In subject 3085, baseline compared to completion was 4:2. In subject 3071 was 4:1. Finally, in subject 3012 baseline was 4, compared to completion score of 1.

CGI-I: Score of 1-2 at completion (week 8). In subject 3175, subject was found to be very much improved. The same went for subject 3085 and 3012. Subject 3071 was found to be much improved.

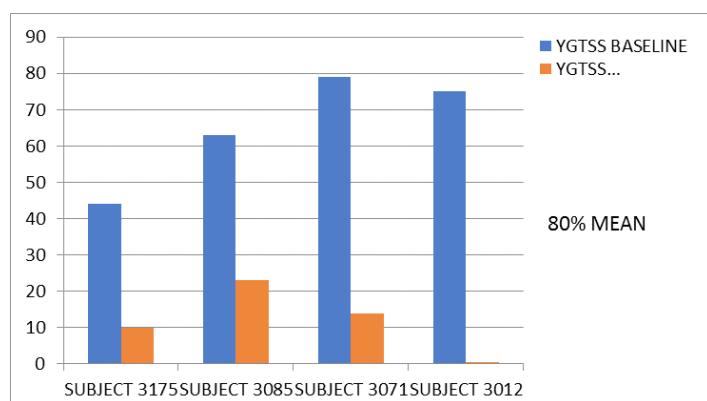


Figure 1: Changes in total TIC score of the Yale Global Tic Severity Scale at Baseline and End Point.

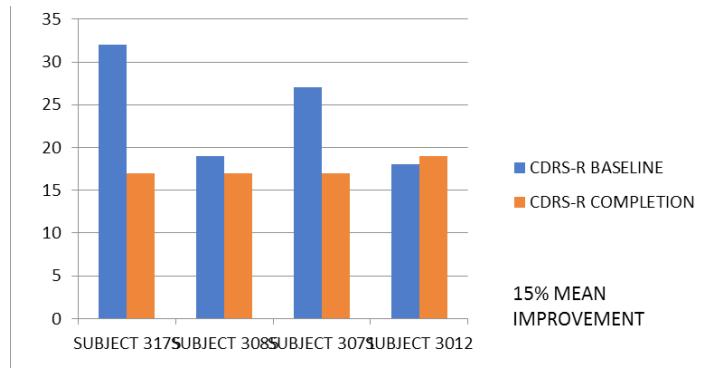


Figure 2: Results of the Children's Depression Rating Scale Revised at Baseline and Endpoint.

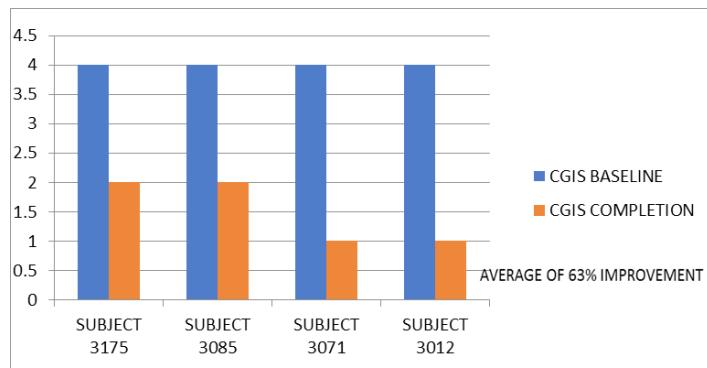


Figure 3: Changes in the Clinical Global Impression Scale for Tourette's Disorder from Baseline to Endpoint.

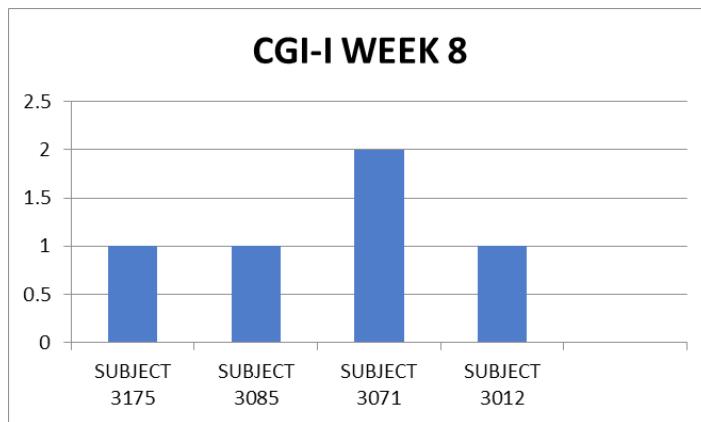


Figure 4: Results of the Clinical Global Impression Improvement for Tourette's Disorder at Endpoint Week 8.

There were no changes in the SAS, AIMS, or BARS from baseline to completion in all four subjects (Score of 0 at baseline and 0 at completion).

CYBOCS: None of the 4 subjects met a diagnosis of OCD.

SNAP-IV: One patient showed a dramatic response in her inattention, impulsivity, hyperactivity and ODD scores from baseline to week 8. Another subject who was diagnosed with ADHD and was receiving a stimulant (Adderall) showed a decrease in his inattention, impulsivity and ODD scores from baseline to week 8.

PARS: There was a decrease in the number of overall anxiety symptoms. There was no significant change in frequency, severity of physical symptoms of anxiety, severity of anxiety symptoms, overall avoidance of anxiety provoking situations, interference with family relationships or performance, interference with peer and adult relationships and/or performance outside the home.

Vital Signs

- Weight: There was an increase in weight in 3 of the 4 subjects and a decrease in weight in one subject between baseline and completion (week 8).
- Waist circumference: 2 subjects showed a decrease in their waist circumference and 2 subjects showed an increase between baseline and completion (week 8).
- Blood pressure and pulse: Supine and standing blood pressure and pulse showed no consistent changes from baseline to completion (week 8).
- ECG: No significant changes.
- Prolactin: Three out of four patients showed a decrease in their prolactin levels.

| Prolactin Levels | | |
|------------------|--------|--------|
| Subject | Screen | Week 8 |
| 3085 | 3.78 | 1.63 |
| 3071 | 1.7 | 1.06 |
| 3125 | 2.75 | 1.98 |
| 3175 | 1.1 | 2.67 |

Table 1: Results of Prolactin Levels at Endpoint.

Discussion

This report is limited because it reports the findings of one site out of 33 sites. However, it was one of the more successfully enrolling sites. There was a robust decrease in the TSS scores from baseline to completion (week 8), an 80% mean decrease in TSS scores from baseline to completion. There is a mean decrease of 63% in the severity of tics as evidenced by CGI-S scores from baseline to completion. There was improvement in the CGI-I from baseline to completion. These findings emphasize the efficacy of Aripiprazole in treating tics in Tourette's syndrome as found in other studies [1,11,17].

The safety and tolerability of Aripiprazole is evidenced by the lack of any significant AE's, specifically extrapyramidal symptoms and akathisia, which are often the result of using typical and some atypical antipsychotics in treating different psychotic disorders (no change in SAS, AIMS, or BARS from baseline to completion) [18-20]. There was no significant change in vitals (BP, HR). There was an increase in weight in 3 out of 4 subjects, and 2 subjects showed an increase in their waist circumference. Of interest is the decrease in the prolactin levels in three of the four subjects. Aripiprazole is not reported to increase the serum prolactin levels because of its mechanism of action [1,2]. Because of the small number of subjects, it is difficult to extrapolate from these findings any significant changes in the PARS or the CDRS, although there was a decrease in the number of anxiety symptoms which was not statistically significant. There was a decrease in the depressive symptoms (one subject had a reduction of 48% from baseline, one subject had a reduction of 37% from baseline) given the mechanisms of action of Aripiprazole with its agonistic property on 5HT1A and antagonistic property of 5HT2A and its use as adjunctive treatment with antidepressants in MDD, one would expect a positive effect on depressive symptoms, which happened with 2 out of 4 subjects. However, the CDRS scores were low at Baseline and the limited number of subjects does not allow for a definitive conclusion.

Conclusion

Four subjects with Tourette's syndrome were treated with Aripiprazole 5-20 mg with a robust decrease of the YGTSS, maintained throughout the study confirming other previous studies

that found Aripiprazole was effective and safe in treating symptoms of Tourette's Syndrome in children and adolescents.

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