

ATOMOXETINE IMPROVES QUALITY OF LIFE AND PATIENT AND FAMILY FUNCTIONING

Results from a double-blind placebo-controlled study in Swedish children and adolescents

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ABSTRACT

Objective: The primary objective was to test the hypothesis that atomoxetine and psychoeducation was superior to placebo and psychoeducation as measured by the Achievement domain of the Children's Health and Illness Profile, Child Edition (CHIP-CE).

Methods: 99 stimulant naive children with ADHD, aged 7-15 years were randomized to atomoxetine (n=49) or placebo (n=50) for 10 weeks of treatment. Simultaneously, the parents participated in four 3-hours group sessions of psychoeducation. The data were analysed using a last observation carried forward change from baseline to endpoint analysis of covariance.

Results: The baseline mean ADHD-RS scores were 38.9 (sd 7.7) and 39.5 (sd 6.7) for atomoxetine and placebo, respectively. Atomoxetine was highly effective in reducing ADHD core symptoms compared to placebo (the Isme-an change from baseline to endpoint was -19.0 for atomoxetine and -6.3 for placebo; p<.001). The following QoL outcomes were statistically significantly better for atomoxetine compared with placebo: The CHIP-CE domains Achievement and Risk avoidance; the total Family Burden of Illness (FBIM) score, the Appraisal of Stress in Child Rearing (ASCR) domain "The child as a burden", and seven of eight "5-15" neuropsychiatric domains: Motor control, Executive function, Perception, Memory, Learning, Social competence, and Emotional/ Behavioral problems. No differences were seen in the patient assessed "I think I am" scale.

Conclusion: Atomoxetine has a positive effect on the QoL for both patients and their families, beyond the reduction of core ADHD symptoms. Significant differences were primarily seen in aspects of improved achievement and interpersonal functioning, rather than in perceived self-image.

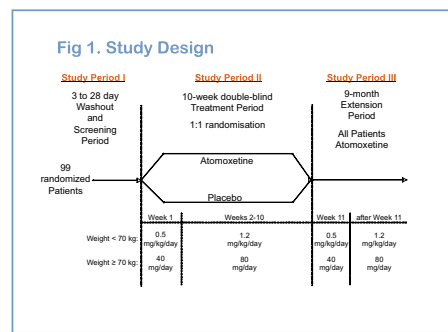
- Children's Depression Rating Scale-Revised (CDRS-R)¹⁴ – Investigator rated
- ADHD Rating Scale - (ADHD-RS) - Investigator Rated
- Clinical Global Impression of Severity (CGI-S) – Investigator Rated
- Clinical Global Impression of Improvement (CGI-I) – Investigator Rated
- Resource utilization (RUQ) – Parent Rated (results not reported here)

Safety

- Vital sign measurements
- Physical examination
- Adverse events reported

Study design

- Double-blind, placebo controlled
- 9 investigative sites in Sweden
- Dosing: Once daily, in the morning



Psychoeducation

Caregivers of participating patients attended four 3-hour sessions of psychoeducation during the double-blind phase each focusing on a main subject:

- What is ADHD and how does it affect the daily life of the child and the family? To adjust the environment by structure, externalizing cues, daily routines and realistic demands.
- To promote positive parent - child interaction and desirable behaviour by clear and supportive communication, prudent consequences, strategic attention, reinforcement and rewards.
- To prevent negative behaviour by planning, problem solving and – when it still occurs - by effective handling.
- Social, school and health services that can be helpful and how to get access to them.

Statistical methods

- All scales analysed using an Analysis of Covariance (ANCOVA) for the change from baseline to Visit 7 (last observation carried forward)
- Models included terms for baseline score, site and treatment
- For the CHIP-CE domains and total score the baseline CDRS score was also included in the model in order to adjust for potential imbalances in this scale at baseline that may affect quality of life
- ADHD-S, CGI-S and CGI-I were also analysed using a mixed models repeated measures analyses as these were collected at all visits
- The effect sizes (ES) were calculated by dividing the model based difference between the groups at each visit by the standard deviation of the corresponding residuals, and by using the LOCF change from baseline to endpoint ANCOVA
- Compliance assessed by direct questioning and upon pill-count, and was defined as taking 70-130 % of the study drug dosage prescribed for that particular visit interval

RESULTS

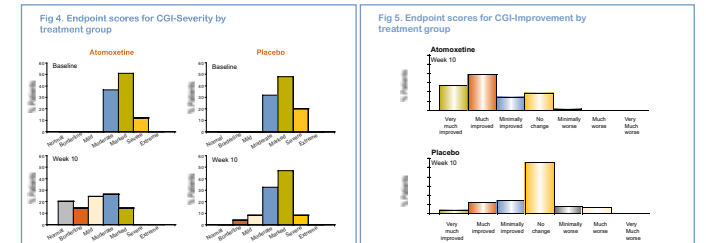
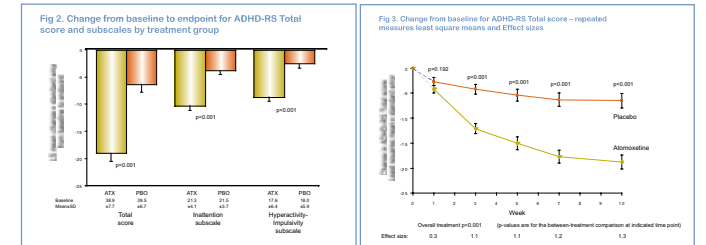
Parameter	Atomoxetine (N=49)	Placebo (N=50)	Total (N=99)
Gender n (%)			
Female	10 (20.4)	9 (18.0)	19 (19.2)
Male	39 (79.6)	41 (82.0)	80 (80.8)
Ethnic origin n (%)			
African	0	1 (2.0)	1 (1.0)
Caucasian	44 (89.8)	49 (98.0)	93 (93.9)
Asian	3 (6.1)	0	3 (3.0)
Other	2 (4.0)	0	2 (2.0)
Age group n (%)			
6 - 11 years	24 (49.9)	32 (64.0)	56 (56.6)
12 - 15 years	25 (51.0)	18 (36.0)	43 (43.4)
Mean Age (SD) years	11.6 (2.3)	11.3 (2.1)	11.5 (2.2)
DSM-IV ADHD subtype n (%)			
Combined	35 (72.9)	39 (79.6)	74 (76.3)
Hyperactive	3 (6.3)	2 (4.1)	5 (5.2)
Inattentive	10 (20.8)	8 (16.3)	18 (18.6)
Comorbid conditions n (%)			
Major depressive disorder	1 (2.1)	2 (4.1)	3 (3.1)
Oppositional/defiant disorder	11 (22.4)	9 (18.0)	20 (20.2)
Tics (any type)	5 (10.4)	7 (14.3)	12 (12.4)
Motoric tics	5 (10.4)	7 (14.3)	12 (12.4)
Phonetic tics	2 (4.3)	6 (12.2)	8 (8.3)

N: total number of patients; n: number of patients with available data.

Medication, treatment compliance, and patient disposition

- The mean doses prescribed at baseline were 0.7mg/kg (SD=0.1), this increased to 1.2 mg/kg (SD=0.2 and 0.1) at weeks 1 and 3 and 1.1 mg/kg (SD=0.2) for the final 5 weeks of double-blind treatment.
- The dose range during the last 7 weeks of the trial was 0.6-1.4 mg/kg.
- At Week 10, 1 patient in the atomoxetine group and 2 patients in the placebo group were not compliant with the dosing regimen.
- No patients discontinued the double-blind phase of the study

Efficacy on core ADHD symptoms



Efficacy on HRQL and other measures of functioning



Appraisal of stress in child rearing (ASCR)

- ASCR includes 8 subscales: Acceptance, Coping, Experiencing problems, Need for a change, Child as a Burden, Managing on One's Own, Pleasure, Relations, and a Global VAS-assessment of Perceived Stress
- The "Child as a burden" and "Coping" subscales showed significant, or a trend, toward improvements in favour of atomoxetine treatment (p<0.007 and 0.069, respectively)

I think I am

No statistically significant differences from baseline to endpoint were found between the treatment groups in any of the subscales: Physical ability, Performance, Psychic wellbeing, Family relations, Relations to peers, and Total score.

Safety

Event Classification	Atomoxetine (N=49)		Placebo (N=50)		Total (N=99)		p-value
	n	%	n	%	n	%	
Headache	19	38.8	9	18.0	28	28.3	0.026
Abdominal pain upper	20	40.8	7	14.0	27	27.3	0.003
Fatigue	16	32.7	9	18.0	25	25.3	0.109
Anorexia	17	34.7	0	0.0	17	17.2	<0.001
Nausea	14	28.6	2	4.0	16	16.2	<0.001
Vomiting	6	12.2	4	8.0	10	10.1	0.524
Irritability	6	12.2	2	4.0	8	8.1	0.159
Depressive symptom	5	10.2	2	4.0	7	7.1	0.268
Upper respiratory tract infection	5	10.2	2	4.0	7	7.1	0.268
Pyrexia	2	4.1	3	6.0	5	5.1	>0.999
Abdominal pain	3	6.1	1	2.0	4	4.0	0.362
Decreased appetite	3	6.1	0	0.0	3	3.0	0.117
Nasopharyngitis	0	0.0	3	6.0	3	3.0	0.242

CONCLUSIONS

- Atomoxetine and psychoeducation was superior to placebo and psychoeducation in several of the HRQL measures and showed a positive effect for both patients and their families, beyond the reduction of core ADHD symptoms
- 7 of 8 "5-15" neuropsychiatric functional domains: Motor control, Executive function, Perception, Memory, Learning, Social competence, and Emotional/ Behavioral problems improved significantly in the atomoxetine and psychoeducation group compared with the placebo and psychoeducation group
- No differences could be assessed in the patient assessed "I think I am" scale.
- In summary, atomoxetine and psychoeducation had a positive effect on the HRQL for both patients and their families, beyond the reduction of core ADHD symptoms
- Potentially, psychoeducation in combination with atomoxetine was the reason for the high effect size of the study. Treatment compliance was very high in both study groups, and no patients discontinued. Since the placebo response was similar to that of other atomoxetine studies without psychoeducation, but higher for the atomoxetine group, psychoeducation may interact positively with pharmacological treatment
- Inclusion of only treatment-naïve patients may have added to the superior efficacy of atomoxetine treatment over placebo, by excluding more treatment-resistant patients
- Atomoxetine treatment was well tolerated with a safety profile in line with the current label

The references below are on the provided handouts

INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) and Health-Related Quality of Life (HRQL)

- 3 % to 7 % of school-aged children are diagnosed with ADHD¹
- ADHD is associated with high risk for elevated rates of antisocial, addictive, mood and anxiety disorders²
- ADHD youths frequently suffer from impairment in school performance, family and peer relations, low self-esteem, and higher proneness for injury, which leads to poor health related quality of life (HRQL)³
- Current treatments of ADHD include pharmacotherapy, preferably in combination with behavioral, and psychosocial interventions⁴
- Effects of treatments on the broader areas of functioning, i.e. not specifically disease-related issues, need further scientific attention⁵
- An additional benefit of improving children's and families' HRQL was demonstrated in registration trials of atomoxetine, a norepinephrine reuptake inhibitor⁶
- A recent randomized 10 weeks open-label study on 201 children and adolescents in UK with ADHD showed superiority for atomoxetine treatment compared to treatment as usual in improving HRQL, as measured with the Child Health and Illness Profile, Child Edition, Parent Reported (CHIP-CE) total score⁷

Objectives

- Primary: to compare the 'broader efficacy' of atomoxetine and psychoeducation vs. placebo and psychoeducation on HRQL in Swedish stimulant-naïve children and adolescents, as measured with the CHIP-CE Achievement domain (covering academic performance and peer relations) from baseline (Week 0) to endpoint (Week 10)
- Secondary: to compare changes of secondary measures of HRQL and functioning: measures of ADHD core symptoms, and measures of resource utilization between the 2 treatment groups

METHODS

Patients

Inclusion Criteria

- Patients aged 7 to 15 years with DSM-IV-defined ADHD as confirmed with Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Parent and Lifetime (K-SADS-PL)
- Minimum severity >1.5 SD for ADHD-RS total score (US norms for age & sex)

Exclusion Criteria

- Previous stimulant treatment
- Symptoms severity requiring immediate therapy
- Weight < 20 kg
- Bipolar or psychotic disorder
- Suicidal risk
- Concomitant psychotropic medication
- Seizure disorder

Measures

Efficacy:

Primary Outcome Measure

- Child Health and Illness Profile-Parent Rated (CHIP-CE): Achievement Domain⁸

Secondary Measures

- CHIP-CE: Risk avoidance, Satisfaction, Comfort, and Resilience Domains⁹, CHIP-CE Total score⁸ - Parent Rated
- Five-to- Fifteen (5-15)¹⁰ - Parent Rated
- Family Burden of Illness Module (FBIM [since 2006 called Family Strain Index, FSI])¹¹ - Parent Rated
- Appraisal of Stress in Child Rearing (ASCR)¹² - Parent Rated
- "I think I am"¹³ - Child Rated