AN OPEN CLINICAL STUDY OF IMMEDIATE RELEASE METHYLPHENIDATE (IR-MPH) VERSUS ATOMOXETINE (ATX) IN ATTENTION DEFICIT HYPERACTIVITY DISORDER

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ABSTRACT

Background: Studies that focus on treatment efficacy with an effectiveness study design provide the best evidence for the practicing clinician regarding the usefulness of treatment methods.

Objective: The present study was carried out to evaluate the effectiveness and tolerability of Methylphenidate (MPH) versus Atomoxetine (ATX) in children aged 8 to 12 years with ADHD.

Design: Open label clinical study

Place and duration of the study: Private psychiatric centre in Mumbai over a period of 2 years from January 2007 to January 2009.

Subjects and Methods: This 12 week, open-label study had 183 subjects on either MPH or ATX. Subjects were titrated to a clinically effective dose of either study medication over 4 weeks and maintained on that dose for an additional 8 weeks. The SNAP-IV parent-rating scale was the primary effective measure used in the study. Other measures used was the Conners Parent rating Scale, Parent Stress Index, IOWA Parent Rating Scale and the Clinical Global Impression Scale for severity and improvement.

Results: MPH showed statistically significant superiority to ATX based on the 18 ADHD symptoms of the SNAP-IV ($p = 0.01$) and severity of ADHD and ODD symptoms ($p=0.008$) as well as on the following secondary assessments. Parental stress too was lower in the MPH group ($p = 0.007$). Both drugs were well tolerated with a similar side effect profile.

Conclusions: The study concluded that MPH is significantly more effective than ATX in reducing ADHD symptoms based on multiple outcome measures in this study group though further studies across different populations are warranted.

Key Words: Methylphenidate, Attention-Deficit/Hyperactivity Disorder (ADHD), Atomoxetine.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a common psychiatric disorder amongst school age children[1]. Recent studies have estimated the worldwide pooled prevalence to be 5.29%[2]. ADHD often progresses into adolescence and puts the child at risk for a large number of comorbid psychiatric illnesses and developmental abnormalities[3-4]. It also has significant educational and social impairment along with a risk for accidents and injury[5] and a significant impact on the utilization of health care resources[6].

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There is confirmatory evidence from various sources that cathecholamine dysregulation is seen in ADHD.[7] US FDA approved medications acting on the noradrenergic and dopamine pathways like immediate release and long acting methylphenidate as well as atomoxetine have been shown to be useful in the treatment of ADHD. Recent studies of these drugs are characterized by large, rigorously diagnosed samples of children and adolescents with ADHD and the use of standardized rating scales as well as extensive safety data. These studies confirm a robust treatment effect size for these agents ranging from 0.7 t0 1.5[8-10]. There are multiple clinical practice guidelines that have been developed for the treatment of ADHD. Despite differences within various guidelines, they all appear to be complementary and not inconsistent. They all recommend a structured approach to diagnosis and treatment, use of medications (stimulants and atomoxetine) with proper follow up and safety evaluations along with an individualized patient based approach and paying adequate attention to comorbidities[11]. The drugs used in the treatment of ADHD (both stimulants and atomoxetine) mark-

edly reduce the inattentiveness, restlessness, hyperactivity and impulsivity seen in children with ADHD[12]. They also improve the overall quality of life, social behavior, and academic performance[13] while they may also reduce aggressive behavior seen in ADHD averting the need for additional pharmacological agents[14].

Multiple studies and meta-analyses support the use of methylphenidate (MPH) in the management of ADHD[15-18]. Methylphenidate though used in the immediate release form for this study is today available in a variety of dosages and different formulations that increases the ease of administration[19]. All forms of methylphenidate preparation have been shown to be safe and efficacious though there has been a recent concern regarding the effects of MPH on growth and cardiovascular parameters along with the development of tics[20-24]. It has been estimated that while most children may benefit from MPH treatment, some children may not tolerate the drug and treatment may thus have to be terminated. Recently the emergence of alternative, safer and effective medications for ADHD has been highlighted[25]. Several non stimulant medications have been used in the management of children with ADHD. Atomoxetine (ATX) is a potent selective inhibitor of presynaptic norepinephrine transporter with minimal affinity for other receptors and transporters[26]. Multiple clinical trials and meta-analyses have documented the safety and efficacy of ATX in the treatment of children with ADHD[27-29]. The magnitude of improvement with atomoxetine treatment as judged by teachers (effect size = 0.6-0.9) is similar to that seen based on investigator interviews with parents (effect sizes = 0.6 to 0.8). However similar effect sizes are also reported with methylphenidate treatment[30]. Recent studies have shown that both ATX and IR-MPH are equivalent in their effects on the symptoms of ADHD with similar results on efficacy parameters[31-32]. It has also been noted that oppositional defiant features, inattention and hyperactivity as symptoms do not affect the response to these drugs[33].

Randomized controlled trials provide the best information, whether a given intervention works but under ideal conditions. Trials for drug efficacy follow set guidelines and use recruited subjects that have no comorbidities so as to determine whether a given treatment works in a specific disorder. Research subjects often differ from the patients seen in routine clinical practice. Effectiveness studies however use the format of a clinical trial but conduct the same in clinical conditions similar to routine clinical practice[34]. The present study is an open clinical study, but set in routine clinical practice to answer which treatment (methylphenidate or atomoxetine) would work better in routine clinical conditions.

SUBJECTS AND METHODS

Subjects / Participants

The study was conducted on physically healthy 8-12 year boys and girls (both ages inclusive) with a documented Diagnostic Statistical Manual – Fourth Edition (DSM-IV) diagnosis of ADHD[35]. This was confirmed by a clinical interview of both parents conducted by the authors. All subjects had to demonstrate significant behavioral difficulties at school and home to be included in the study. Subjects were either off medication or on ADHD medication but yet showed a baseline Clinical Global Impression (CGI) – severity score of 4 or more[36]. To mimic clinical settings, any other medication used to treat non ADHD disorders or symptoms or psychological / behavioral interventions were permitted as long as the intervention had been stable over a period of 6 weeks prior to the study. No change in intervention or start of a new treatment was allowed during the study period. None of the children were on antidepressant therapy. Written informed consent was obtained from the parents of all children in the study.

Exclusion criteria

1. Participants who after sufficient trial (6-8 weeks) were non-responders to MPH or had adverse effects as a result of MPH in the past.
2. Marked anxiety, agitation, aggression or mood swings if present as per clinical interview.
3. Presence of glaucoma, seizure disorder, psychotic episodes (past or present), psychotic disorder, bipolar disorder, mental retardation and learning disability.
4. Presence of tics or Tourette's disorder and a family history of the same.
5. Presence of any physical illness that would be affected by the medication in the study or any unstable medical illness under treatment.
6. History of or current eating disorder (Anorexia nervosa, Bulimia nervosa or binge eating disorder), in the participant.
7. History of any form substance or medication abuse.

Study Design

The study was a 12 week open clinical study where the participants received IR-MPH or ATX prescribed as per the clinician's discretion and on the basis of the clinical requirement of the subject unlike randomization lists in most drug trials. IR-MPH was started at whatever dose was felt appropriate by the clinician. Over 4 weeks each dose was titrated weekly by 5mg or 10mg increments based on the investigator's judgment up to a maximum dose of daily dose of 50mg per day. ATX was started at 10mg per day and was increased by 5mg or 10mg weekly

increments and a maximum dose of 60mg per day was permitted. The study protocol required the subject to be on his optimal dose of either drug for the last 6 weeks of the study. Dose reductions in the wake of emerging side effects were permitted. Written consent was obtained from the parents prior to the study. There were three study visits – baseline, 6 weeks and 12 weeks. Clinical check visits were scheduled fortnightly and frequent visits if needed were allowed. Caregivers would have to purchase medication from the pharmacy themselves and subjects were allowed to remain in the study even if they missed a few doses of medications (2-5 doses). Both the investigators and patients were aware of the medication they were on as this was an open study and this may have led to an element of bias during further interpretation. Dosage used was either once or twice a day.

Measures used in the study

1. The main tool used as an outcome measure was the Swanson, Nolan and Pelham – fourth edition (SNAP-IV) rating scale that contains 18 ADHD items and 8 oppositional defiant disorder (ODD) items. Each item is scored for severity on a 4-point scale (0 = not at all and 3 = very much). This was rated by the parents[37].
2. The 27-item Conners Parent Rating Scale (CPRS) – short form scored on 4-point scale (0 = not true at all and 3 = very much true)[38].
3. The 10-item Inattention / Overactivity with Aggression (IOWA) Conners Parent Rating Scale scored on a 4-point scale (0 = not at all and 3 = very much)[39].
4. The Parent Stress Index (PSI) a 36 item scale, which was rated on a 5-point scale (1 = strongly agree to 5 = strongly disagree)[40].
5. Physician rated Clinical Global Impression of Severity (CGI-S) and Clinical Global Impression of Improvement (CGI-I) rated on a 7 point scale[36].

Statistical Analysis

Baseline demographics and safety outcomes were summarized for all subjects who took at least one dose of the trial medication. Effectiveness analyses was performed on an intent to treat sample consisting of all subjects who took at least one dose of trial medication and had at least one protocol mandated post baseline assessment. The end-point was defined as the last protocol mandated post-baseline observation carried forward (LOCF). Analyses were conducted at week 6, week 12 and end-point. End point was 1 week after the 12 week duration. The SNAP-IV rating scale was used to assess two outcomes – the first 18 ADHD items (SNAP-IV-18) and the entire 26 items (ADHD + ODD) (SNAP-IV-26). Analysis of variance (ANOVA) was the main statistical measure used for all the rating scales in the study. The CGI-S and CGI-I were assessed by the Van Elteren test. The entire statistics were carried out by a blind independent statistician who was paid his fees separately and was not a part of the study as an investigator.

The SNAP-IV rating scale was used to specify two effectiveness outcomes –

(1) Remission of symptoms on end point (which was defined as a score of 0 or 1 on each of the first 18 ADHD items) referred to as SNAP-IV-18[41].

(2) Change from baseline at the study end point in scores on the total 26 items (ADHD + ODD) referred to as SNAP-IV-26.

The remission rates were analyzed by the independent and blind biostatistician using the Cochrane Mantel Haenszel test of general association.

RESULTS

During a two year period (January 2007 to January 2009), a total of 289 subjects were screened of whom, 183 subjects who met the study criteria. Based on clinical judgment and requirement clinically by the patient they were started on either MPH-IR or ATX. There were a total of 91 subjects on MPH while 92 were on ATX. All were included in the safety and baseline analysis. The subjects in both groups were similar in baseline characteristics (Table 1) and mean baseline scores for all effectiveness measures (Tables 2a, 2b and 2c). 161 subjects completed the 12 week trial. 12 subjects in the MPH group and 10 subjects in the ATX group discontinued prematurely. The reasons were adverse events (n=8 MPH, n=5 ATX), consent withdrawal (n=2 MPH, n=2 ATX) and protocol violators (n=2 MPH, n=3 ATX).

At the end point of the study, the mean daily dose of MPH was 29.3 ± 13.3 mg with 61% on a BID dose and 39% on a TID dose (no dosage after 6pm). The mean daily dose of ATX at the end point was 35.6 ± 16.9 mg with 95% on a BID dose (morning and afternoon) while 5% was on a single morning daily dosage. The mean duration of treatment was 79.4 ± 12.2 days for MPH subjects while it was 78.9 ± 13.3 days for ATX subjects. The percentage of subjects that missed a dose was lower in the ATX group being 55 (59.78%) compared to 71 (78.02%) in the MPH group. The mean total number of doses missed was less overall being 2.02 ± 3.3 for ATX (range 1 – 8) while it was 2.8 ± 4.4 for MPH (range 1 -9).

Results after analysis of the SNAP-IV scores

At end point, remission was achieved by 48% of MPH subjects compared to 26% of the ATX subjects. Remission rates were higher at week 6 (39%) and week 12 (51%) in the MPH compared to 15% (week 6) and

Table 1

Characteristics of subjects in the trial

Feature	MPH group (n = 91)	ATX group (n = 92)
Age at Screening(Mean ± SD)	9.2 ± 2.2(6-12 years)	9.0 ± 2.4(6-12 years)
Age at Diagnosis(Mean ± SD)	8.0 ± 2.1(4-12 years)	8.3 ± 2.3(4-12 years)
Diagnosis	n (%)	n (%)
ADHD inattentive type	9 (9.89)	7 (7.6)
ADHD hyperactive impulsive type	77 (84.62)	81 (88.04)
ADHD combined type	5 (5.49)	4 (4.35)
Comorbidity	n (%)	n (%)
Conduct Disorder	3 (3.3)	2 (2.17)
Oppositional defiant disorder	41 (45.05)	44 (47.83)
Others*	3 (3.3)	3 (3.26)
Gender	n (%)	n (%)
Males	76 (83.52)	79 (85.87)
Females	15 (16.48)	13 (14.13)

* Other co-morbidities include in the ATX group – 2 children had pica (eating clay) and one had habit disorder (nail biting). In the MPH group 2 children had pica (eating mud and clay), 1 had fungal infection of the nails (not under treatment during the study neither previously).

Table 2a

Summary statistics and analysis of SNAP-IV

Effectiveness Measure	Mean Baseline Score and Change from Baseline Score (± Sd)		ANOVA p value
	MPH	ATX	
SNAP-IV 26 items (ADHD + ODD) scale			
Baseline	55.6 ± 12.3	54.4 ± 12.6	
Week 6	-27.6 ± 14.3	-20.6 ± 15.3	0.033*
Week 12	-25.6 ± 14.6	-17.6 ± 13.3	0.008*
End point	-25.9 ± 15.3	-17.8 ± 13.5	0.007*
SNAP-IV 18 items (ADHD) scale			
Baseline	39.6 ± 9.3	38.8 ± 9.1	
Week 6	-18.3 ± 12.1	-14.6 ± 11.3	0.06
Week 12	-17.6 ± 12.2	-13.6 ± 11.0	0.01*
End point	-18.7 ± 12.4	-14.8 ± 11.6	0.01*

SD = standard deviation, ANOVA = analysis of variance * p d" 0.05

Table 2b

Summary statistics and analysis of the other measures

Effectiveness Measure	Mean Baseline Score and Change from Baseline Score (± Sd)		ANOVA p value
	MPH	ATX	
IOWA Conners Parent Rating Scale			
Baseline	21.2 ± 6.3	20.6 ± 6.6	
Week 6	-9.6 ± 7.3	-7.6 ± 6.2	0.04*
Week 12	-9.7 ± 6.9	-7.5 ± 6.4	0.03*
End point	-9.4 ± 7.1	-7.8 ± 6.6	0.04*
Conners Parent Rating Scale – short form (CPRS)			
Baseline	55.9 ± 15.3	566 ± 14.7	
Week 6	-28.6 ± 18.3	-20.9 ± 15.7	0.015*
Week 12	-25.3 ± 17.8	-18.6 ± 14.8	0.006*
End point	-28.6 ± 16.3	-19.4 ± 15.2	0.003*
Baseline	115.8 ± 22.8	117.8 ± 23.1	
End point	+15.6 ± 19.3	+10.6 ± 15.6	0.007*

SD = standard deviation, ANOVA = analysis of variance * p d" 0.05

Table 2c

Summary statistics and analysis of the CGI scales

Effectiveness Measure	Mean Baseline Score and Change from Baseline Score (± Sd)		ANOVA p value
	MPH	ATX	
Clinical Global Impression – Severity (CGI-S) scale			
Baseline	5.2 ± 0.7	5.6 ± 0.6	
Week 6	-1.9 ± 1.3	-1.5 ± 1.3	0.04*
Week 12	-2.3 ± 1.1	-1.3 ± 1.2	0.03*
End point	-2.4 ± 1.1	-1.4 ± 1.2	0.04*
Clinical Global Impression – Improvement (CGI-I) Scale (Mean ± SC)			
Week 6	2.6 ± 1.3	2.8 ± 1.7	0.129
Week 12	1.8 ± 1.2	2.3 ± 1.8	0.0002*
End point	1.9 ± 1.3	2.4 ± 1.6	0.0003*

SD = standard deviation, * p d" 0.05,

Van Elteren test used in statistical analysis

Table 3

Number (%) of subjects reporting adverse events

Adverse Event Type	MPH (n = 91)	ATX (n = 92)
All events	56 (61.54)	43 (46.73)
List of specific side effects reported		
Decreased appetite	22 (24.18)	24 (26.09)
Headache	5 (5.49)	3 (3.26)
Insomnia	8 (8.79)	2 (2.17)
Nervousness	1 (1.1)	1 (1.09)
Abdominal pain	1 (1.1)	—
Agitation	9 (9.89)	2 (2.17)
Emotional symptoms*	7 (7.69)	3 (3.26)
Fatigue	4 (4.4)	1 (1.09)
Flu like symptoms	1 (1.1)	1 (1.09)
Vomiting	2 (2.2)	—
Diarrhea	—	1 (1.09)
Other sleep problems	1 (1.1)	3 (3.26)
Dullness ^	—	1 (1.09)
Irritability***	4 (4.4)	1 (1.09)

* Emotional symptoms included increased impulsiveness, stubbornness, mood swings, sensitivity to comments and crying spells.

** Other sleep problems included nightmares (1 in MPH, 1 in ATX) and 2 reported excessive daytime sleepiness in the ATX group. These 2 from the ATX group withdrew from the trial due to adverse events.

*** Irritability was a feeling of irritation or losing temper over trivial issues throughout the day.

^ Dullness was defined as a clouded feeling where the patient felt no desire and lack of clarity mentally when working or slowness in thought process (like one feels after recovery from a viral infection or during the same)

28% (week 12) for ATX respectively. Statistically significant treatment differences were noted at every point of time for MPH compared to ATX i.e. at week 6 (p =0.033) and at week 12 (p = 0.007) (Table 2a) on all 26 items of the SNAP-IV. Significant differences were also noted in the scores on only ADHD symptoms (SNAP-IV-18) for week 12 (p = 0.01) in favor of MPH over ATX. Differences though noted were not significant in this regard at week 6. End point was 1 week after the 12 week period.

Results on the other measures –

Statistically significant differences at the end point were noted in favour of MPH on the IOWA Conner (p = 0.04), Conners Parent Rating Scale (p = 0.003) and the Parent Stress Index (p = 0.007) (table 2b). Similar trends followed for Clinical Global Impression – Severity (p = 0.0001) and Improvement scales (p = 0.0003) (Table 2c).

Adverse events –

Adverse events were reported in 54.1% subjects across both the groups. More subjects reported insomnia and agitation as a side effect with MPH compared to the ATX group. All other adverse events were similar between the two groups. The adverse events were mild to moderate severity and no serious adverse event was reported in either group. At each visit heart rate and blood pressure were measured but were not analyzed in the study. No medically significant changes in these parameters were noted in any of the patients.

DISCUSSION

The current study demonstrates treatment with

MPH, when compared with ATX resulting in a greater percentage of cases that achieve remission of ADHD symptoms. In a previous study between the two drugs ATX was found to be equivalent to MPH but however demonstrated more treatment emergent adverse events[42]. The same has been noted in a recent study comparing ATX and OROS-MPH[43]. A meta analyses study using articles between 1966 and 2005 has revealed that the available evidence shows MPH to be the first line and more acceptable drug of choice for ADHD. ATX is considered a second line drug when MPH does not give us the desired response or in patients who develop adverse events due to MPH[31]. An older study shows ATX showing similar results to immediate release MPH when managing ADHD symptoms[44].

Other issues in questions are dosing as well as trajectory of response. Our study has incorporated a twice daily or once daily dosage for either drug. Studies with ATX have shown a twice daily dosage to better while some say a higher once daily higher dose is equally efficacious[45]. Some studies mention to response to ATX is gradual and one needs to exert patience over 12 weeks for full response and total effect may be gauged by 16 weeks compared to MPH where effects may be evident in the 1st week itself. However with a rapid titration schedule like our study some previous trials have demonstrated good response to ATX in 1 week of treatment[46]. In our study a good response was seen to either drug in 6 weeks itself. This is in keeping with what has been observed in routine clinical practice by us.

For the present study we had excluded children who did not tolerate MPH in the past or were non responders to MPH. Studies have shown that ATX shows a diminished effect in a group of children who have not responded to ATX[43]. while there are other studies that have shown a good response for ATX in MPH non responders[29,47]. Lack of MPH non responders in our study group could have been a factor for good response to ATX. The present study shows IR-MPH to be superior to ATX on all major outcome measures. This is in keeping with major ADHD treatment meta-analyses and guidelines which show MPH as a first line of treatment[32-33].

Most trials of both these drugs are not beyond 12 weeks[48]. Studies longer than 12 weeks will probably give us a chance to assess the full response and tolerability of both drugs. Long-term studies of children with enhanced symptomatic remission will be required to ascertain if the expected beneficial changes in adulthood are manifested, and decrease the risk of potential long-term consequences such as excessive smoking and drinking[49].

The adverse event profiles encountered during the study matched that of previous studies and reviews[50]. Sleep related side effects seen in our trial have been replicated in a previous study[51]. Flexibility in dosing as in our study along with an open study protocol could have accounted for a lower adverse effect profile. We did not measure any major cardiovascular parameters in the analysis. We also did not look at the effect on growth due to the shorter duration of the study. Both ATX and MPH have been well tolerated in previous studies of similar duration[29,52-54].

The child who experiences complete and sustained remission from ADHD symptoms may have better opportunity to benefit from non-pharmacological evidence-based treatment programs and also have better long term outcomes[41]. The present study bearing these implications used remission as one of the parameters to compare the two drugs and found better remission rates with MPH compared to ATX. Since the rating scales were parent rated, there may have been some biases in the reporting process.

Parents of children with ADHD exhibit stress have less self-esteem and are at greater risk for depression and other types of personal distress[55]. Our results reveal a significantly greater decrease in parental stress in the MPH group than in the ATX group. These changes may provide an optimistic family atmosphere meaning well for the social reintegration of the child within his peer group.

Our study documented the extent of symptomatic remission, improvement in symptoms across various rating measures and reduction in parental stress with both drugs. The results of this study should be viewed as an important initial step, which in conjunction with relevant other treatment interventions, demonstrate how medications offer patients with ADHD a way to improve overall functioning. This study has been one that compares IR-MPH and ATX as these are the standard treatments for ADHD in India. Once a day MPH has just been launched in 2011 here and no other form of MPH is yet available. Further long term studies between these two compounds are warranted.

LIMITATIONS

The present clinical study was not blinded. A double blind design would have negated the objective of providing data on effectiveness in everyday clinical practice settings. The differences between the two groups on a wide variety of different outcome measures suggests that the findings are unlikely to be explained by a 'halo effect' alone. Parent and non- blinded clinician ratings of the scale is another confounding factor. Both the medications showed an early response and did not show a major response over time. The study did not look at the stigma associated with medication use as well as peer acceptance improvements after medications. Addressing these factors would have been a useful addition to the findings from the study. Lack of physiological parameters being monitored in the adverse effects rating is another limitation.

One of the most obvious limitations is the lack of teacher ratings. Although children spend a great deal of

time in school and the DSM-IV definition of ADHD requires evidence of difficulty in school as well as home settings. Our study hypothesis focused solely on the evaluation of behavior by parents as these were patients attending a psychiatric clinic, which rendered teacher ratings not applicable in our study construct. Contacting various teachers from different schools may have been a difficult task to complete the study considering the number of subjects.

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