

# Comparative efficacy of methylphenidate and atomoxetine in oppositional defiant disorder comorbid with attention deficit hyperactivity disorder

Jasmin Garg, Priti Arun, BS Chavan

Department of Psychiatry, Government Medical College and Hospital, Sector 32, Chandigarh, India

## ABSTRACT

**Background:** Oppositional defiant disorder (ODD) is frequently comorbid with attention deficit hyperactivity disorder (ADHD) and is associated with substantial functional impairments. Methylphenidate and atomoxetine are well-established drugs for the management of ADHD. Some studies from Western countries have reported these drugs to be effective in the management of ODD comorbid with ADHD. This study aimed to assess if methylphenidate and atomoxetine are efficacious in treating Indian children with ODD comorbid with ADHD. **Subjects and Methods:** In this prospective, open-label study, 37 patients of age 6–14 years with a diagnosis of ODD comorbid with ADHD randomly received either methylphenidate (dose 0.2–1 mg/kg/day) or atomoxetine (dose 0.5–1.2 mg/kg/day) for 8 weeks. Improvements in ADHD and ODD symptoms were assessed using Vanderbilt ADHD diagnostic parent rating scale (VADPRS). **Results:** At 8 weeks, there were statistically significant improvements in both ADHD and ODD symptoms in both methylphenidate and atomoxetine groups, as per VADPRS. The improvements produced and tolerability was comparable in the two groups. 80% of the patients from methylphenidate group and 64.3% patients from atomoxetine group ceased to fulfill the criteria for the presence of ODD at 8 weeks. **Conclusions:** Methylphenidate and atomoxetine are effective in the treatment of ODD comorbid with ADHD in short duration.

**Key words:** Atomoxetine, attention deficit hyperactivity disorder, methylphenidate, oppositional defiant disorder

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## INTRODUCTION

Oppositional defiant disorder (ODD) consists of recurrent uncooperative, disobedient, and hostile behavior which is not accounted for by the developmental stage of the child. It is defined in DSM-IV-TR as an enduring pattern of negativistic, defiant, and disruptive behavior toward authority figures. It

must be present for more than 6 months and must not be caused by psychosis or a mood disorder, and the behavior must negatively impact the child's social, academic, or occupational functioning. It does not include the most aggressive aspects of conduct disorder which is directed toward people, animals and property.<sup>[1]</sup> Negativistic and defiant behaviors are expressed by persistent stubbornness, resistance to directions, and unwillingness to compromise, give in or negotiate with adults and peers. It may also involve deliberate and persistent testing of limits, usually by ignoring orders, arguing, and failing to accept blame for misbehavior. ODD is among the most common mental health conditions in childhood. The prevalence of ODD in the general population has been reported to be between 2% and 16%. It has been estimated that around 60% of patients with ODD will develop conduct disorder and will have high risk for substance abuse.<sup>[2]</sup> Children with ODD have substantially impaired relationships with parents, teachers, and peers. These children are not only impaired in comparison with their peers, but they also show greater

Address for correspondence: Dr. Jasmin Garg,  
Department of Psychiatry, 5<sup>th</sup> Level, D-Block, Government Medical  
College and Hospital, Sector 32, Chandigarh, India.  
E-mail: jasmin.arneja@gmail.com

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social impairment than do children with bipolar disorder, depression, and anxiety disorders.<sup>[3]</sup>

Oppositional defiant disorder has a high co-occurrence with attention deficit hyperactivity disorder (ADHD). In 35–65% of patients with ADHD, ODD is also part of the clinical picture.<sup>[4]</sup> Children with ADHD and comorbid ODD tend to experience more severe ADHD symptoms, greater functional impairment and poor quality of life than children with ADHD alone.<sup>[5]</sup> This means that families are under high levels of stress, dealing with several difficult behaviors.

Several studies from Western countries have shown that psychostimulants like methylphenidate are effective in ODD patients with comorbid ADHD. In a meta-analysis of 28 studies, it was reported that stimulants are effective in overt and covert aggression-related behaviors in ADHD in a short-term.<sup>[6]</sup> Atomoxetine is a selective norepinephrine reuptake inhibitor approved for the treatment of ADHD since 2002.<sup>[7]</sup> Atomoxetine has also been used in the management of ODD comorbid with ADHD as some studies have evaluated its efficacy in a short term.<sup>[8-13]</sup> These studies have reported mixed results about improvements in ODD symptoms. However, there are no data from India. Hence, the present study was carried out to find out if methylphenidate and atomoxetine are efficacious in the treatment of ODD comorbid with ADHD.

## SUBJECTS AND METHODS

Patients were inducted from those attending the Child Guidance Clinic of a tertiary care hospital in North India from October 2010 to May 2012. This study is a subset of another trial which aimed to assess the efficacy of methylphenidate and atomoxetine in symptom reduction of ADHD. Patients of 6–14 years age, with a diagnosis of ADHD, according to DSM-IV-TR were recruited for the trial. These patients were administered the Vanderbilt ADHD Diagnostic Parent Rating Scale (VADPRS)<sup>[14]</sup> to screen for the presence of comorbid ODD. The patients with the diagnosis of ODD with comorbid ADHD were taken up in the present study. It was a prospective, randomized, open-label study. Children were brought by parents or referred by school to the Child Guidance Clinic. Patients with a history of nonresponse or adverse drug reactions to either methylphenidate or atomoxetine and the patients who had taken any medication for ADHD in the past 1-month were excluded. In addition, the patients with a history of heart disease, seizures, pervasive developmental disorder, substance abuse, mental retardation, or tic disorder were also excluded. Before initiating treatment, electrocardiogram was performed for each patient to rule out any cardiac abnormality.

The patients were allotted to two groups as per computer-generated table of random numbers (group A and group B). Patients of group A received immediate release tablet methylphenidate (once or twice daily) and group B received tablet atomoxetine (once or twice daily). The initial sample consisted of 69 ADHD patients randomized into methylphenidate and atomoxetine groups. Of 69 patients with ADHD, 15 from methylphenidate group and 22 from atomoxetine group fulfilled the criteria for the presence of comorbid ODD, and these were included in the analysis of the present study [Figure 1].

Patients were started on tablet methylphenidate (immediate-release) 5 mg OD or tablet atomoxetine 10 mg OD on their first visit. Efforts were made to increase the dose of methylphenidate up to 1 mg/kg/day and of atomoxetine up to 1.2 mg/kg/day once or twice daily depending upon the response and tolerability. Weekly increments of 5 mg were tried for both methylphenidate and atomoxetine. Patients were assessed at baseline and once weekly till 8 weeks. The patients who could not come for weekly follow-up, were assessed fortnightly. On each visit, improvement in symptoms of ADHD and ODD was assessed by VADPRS. The various side effects were noted on each assessment on the Adverse Events Checklist prepared for the study. Patients who developed intolerable side effects were taken out of the study. They were then managed as per standard departmental protocol. Written and informed consent was obtained from both parents/guardians and the

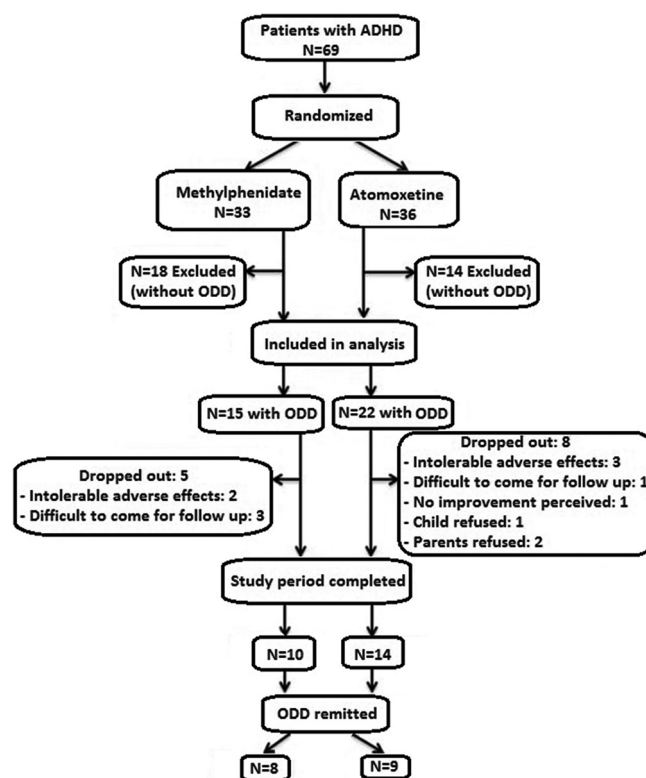


Figure 1: Patient flowchart

children. Clearance was sought from the ethics committee of the institution. The trial was registered in clinical trial registry, India with registration number CTRI/2011/08/001981.

### Statistical analysis

Data were analyzed using SPSS (version 16.0. Chicago, SPSS Inc., 2007), and it was represented in mean and (standard deviation). Significance level was  $P < 0.05$  (two-tailed). Fisher's exact test and Chi-square test were used to compare categorical variables. Mann-Whitney test and Wilcoxon signed rank test were used for analysis of nonparametric data.

## RESULTS

At baseline, methylphenidate and atomoxetine groups were comparable with regard to mean age and sex distribution. In both the groups, males outnumbered the females for the presence of ODD, the combined type of ADHD was the most common, followed by inattention type and hyperactive/impulsive type. Chi-square test was used to assess whether the two groups were comparable with respect to the number of patients with any of the three types of ADHD, and no significant difference was found. Patients were also screened for the presence of depression and anxiety, but none fulfilled the criteria for the same. The baseline VADPRS total score and VADPRS subscale scores (inattention, hyperactivity and ODD) were comparable between the two groups on the Mann-Whitney test [Table 1].

**Table 1: Comparison on baseline characteristics**

Variable	Methylphenidate n=15	Atomoxetine n=22	P
Age in years (mean±SD)	8.73±2.40	9.05±2.59	0.713
Sex			
Male	12	17	0.843
Female	3	5	
Type of ADHD <sup>†</sup>			0.858
Inattention	3	3	
Hyperactive/impulsive	1	2	
Combined	11	17	
VADPRS (mean±SD) <sup>‡</sup>			
Total	57.00±8.66	62.73±10.68	0.125
Inattention	21.20±3.66	20.73±4.56	0.988
Hyperactivity	18.33±6.83	20.91±6.23	0.120
ODD <sup>§</sup>	14.33±3.33	15.09±3.86	0.607

<sup>†</sup>Attention deficit hyperactivity disorder; <sup>‡</sup>Vanderbilt ADHD diagnostic parent rating scale; <sup>§</sup>Oppositional defiant disorder

Five patients in the methylphenidate group and 8 in the atomoxetine group dropped out in the course of study. Various reasons for drop outs are shown in Figure 1. There was no statistically significant difference between the reasons for drop-outs between the two groups on the Chi-square test ( $P = 0.349$ ). The adverse effects which lead to drop out were reduction in appetite, headache, irritability in both the groups; drowsiness and sadness in the atomoxetine group and fatigue in the methylphenidate group.

Improvement in ADHD symptoms and ODD symptoms as measured on VADPRS score was assessed using Wilcoxon signed rank test as data was not normally distributed. Highly significant difference was found in VADPRS scores in both the groups after 8 weeks. The mean VADPRS (total and subscales) scores were compared in methylphenidate and atomoxetine groups using Mann-Whitney test at 8 weeks and no statistically significant difference was found [Table 2].

At 8 weeks, according to VADPRS, 8 children out of 10 (or 80%) ceased to fulfill the criteria for the presence of ODD in the methylphenidate group. Similarly, in the atomoxetine group, out of 14 children, 9 children (or 64.3%) ceased to have symptoms of ODD at 8 weeks [Figure 1].

The average dose administered at 8 weeks was 15.41 mg/day (or 0.490 mg/kg/day) in methylphenidate group and 17.21 mg/day (or 0.672 mg/kg/day) in atomoxetine group. According to the adverse effects checklist prepared for the study, a total of 7 (46.6%) patients from methylphenidate group and 12 (54.5%) from atomoxetine group developed some side effect during the course of the study. The various adverse effects reported by the patients in two groups are listed in Table 3. These were compared between both groups, and no significant difference was found on the Chi-square test. In addition, one case each reported insomnia and pain abdomen in the methylphenidate group. Similarly one case each reported nausea, vomiting, and sadness in the atomoxetine group.

## DISCUSSION

In the present study, ODD was present in 53% of patients with ADHD. Majority of the children were males, the similar

**Table 2: Change in VADPRS scores from baseline to 8 weeks**

VADPRS score <sup>‡</sup>	Methylphenidate (mean±SD)			Atomoxetine (mean±SD)			Intergroup P
	Baseline n=15	Week 8 n=10	P	Baseline n=22	Week 8 n=14	P	
Total	57.00±8.66	24.40±9.00	0.005**	62.73±10.68	27.79±20.38	0.001**	0.838
Inattention	21.20±3.66	8.30±3.71	0.005**	20.73±4.56	9.86±6.81	0.001**	0.906
Hyperactivity	18.33±6.83	8.80±5.80	0.005**	20.91±6.23	10.14±8.07	0.002**	0.814
ODD <sup>§</sup>	14.33±3.33	6.40±3.23	0.005**	15.09±3.86	6.36±5.01	0.001**	0.929

<sup>‡</sup>Vanderbilt ADHD diagnostic parent rating scale; <sup>§</sup>Oppositional defiant disorder; \*\* $P < 0.01$ : Highly significant

**Table 3: Comparison of adverse effects in methylphenidate and atomoxetine groups**

Adverse effects	Methylphenidate n=15 (%)	Atomoxetine n=22 (%)	P
Decreased appetite	5 (33.3)	7 (31.8)	0.923
Irritability	2 (13.3)	5 (22.7)	0.474
Drowsiness	1 (6.7)	4 (18.2)	0.314
Headache	1 (6.7)	2 (9.1)	0.791
Fatigue	2 (13.3)	1 (4.5)	0.336
Urinary incontinence	1 (6.7)	1 (4.5)	0.779

findings have been reported in earlier studies.<sup>[2]</sup> The results showed that both methylphenidate and atomoxetine were highly effective in reducing the symptoms of ODD. Earlier short-term placebo-controlled trials of methylphenidate for ODD comorbid with ADHD have also shown it to be effective.<sup>[15-18]</sup> Some previous studies found atomoxetine to be superior than placebo in improving ODD symptoms,<sup>[11-13]</sup> while others did not.<sup>[8-10]</sup> The dose of atomoxetine administered to the patients in the present study was well within the prescribed limit for management of ADHD.<sup>[7]</sup> It was unlike the findings of a previous study which reported that higher dose of atomoxetine was required to produce improvements in patients with ADHD comorbid with ODD, than those with ADHD alone.<sup>[11]</sup>

In this study, 80% of the patients in the methylphenidate group failed to fulfill the criteria for diagnosis of ODD at the conclusion of the study. This was also concordant with findings of an earlier study where methylphenidate treatment in the short-term lead to remission of ODD in 9 out of 10 children.<sup>[19]</sup> In the atomoxetine group, 64.3% patients had remission of symptoms of ODD. The remission of ODD has not been directly evaluated in previous placebo-controlled trials of atomoxetine. The two drugs produced comparable improvements in symptoms of ODD. Both the drugs were equally tolerated in relation to the development of adverse effects. The rate of occurrence of adverse effects was also consistent with results of some previous comparative trials of methylphenidate and atomoxetine in ADHD.<sup>[20]</sup>

This study had certain limitations. It was an open label trial, and placebo arm was not included due to ethical reasons. The improvement produced by both the drugs in ODD symptoms might imply that defiant and hostile behaviors were an integral part of ADHD and improvement in ADHD also led to improvement in ODD symptoms. Furthermore, the follow-up period was short, and it needs to be seen whether improvement in ODD symptoms sustains over the long period.

Nevertheless, this is the first study from India comparing efficacy of atomoxetine and methylphenidate in ODD comorbid with ADHD. The study indicates that ODD comorbid with ADHD

shows considerable improvement with both methylphenidate and atomoxetine and symptoms of ODD remits in majority with short duration of treatment. Both drugs had comparable efficacy and good tolerability.

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