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# Risk of Suicidal Events in Youths Taking Atomoxetine Compared with Those on Methylphenidate; An Observational Cross-Sectional Study

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**ABSTRACT**

***Background:*** Stimulants such as methylphenidate and atomoxetine, a nonstimulant norepinephrine reuptake inhibitor, are approved for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Associations between the use of methylphenidate or atomoxetine with suicidal ideation and suicide-related behavior have been reported in the literature. The present study aimed to compare the effects of atomoxetine with that of methylphenidate on suicidal ideation and behavior in children and adolescents.

***Methods:*** Children and adolescents between 7 to 17 years of age with the diagnosis of ADHD, based on DSM-5 criteria, were included in this observational, cross sectional study. The suicidal ideation was assessed among children and adolescents who have been receiving either atomoxetine or methylphenidate for at least 12 months prior to entering the study. A Farsi version of Positive and Negative Suicide Ideation (PANSI) inventory was applied for the assessment. Differences among age groups, duration of therapy and comparison of positive and negative scores in both genders were analyzed using t-test. In addition, a one-way analysis of variance (ANOVA) was applied to examine the differences in positive and negative scores among different age groups. Moreover, chi-square and Fisher's exact tests were performed to examine the effects of past history of drugs and other present illnesses on suicidal ideation. P-value of $<0.05$ was considered as significant.

***Results:*** A total of 57 students between 7 to 17 years of age were enrolled in this study. Twenty-eight patients have been taking atomoxetine at doses of 10 to 60 mg/day while 29 were on methylphenidate 7.50-55 mg/day. The mean positive and negative scores in the atomoxetine group were found to significantly differ (P=0.001) from those in the methylphenidate group. No risk of suicidal ideation was detected in the atomoxetine group, while in the methylphenidate group 15 out of 29 patients (51.7%) scored above the cutoff point. In terms of the relationship between suicidal ideation and history of other drugs prior to the current therapy and other concurrent disorders, chi-square test showed no significant difference in methylphenidate group (P=0.100 and 0.500 respectively). This analysis was not considered in atomoxetine group due to the absence of suicidal ideation.

***Conclusion:*** The authors of this study suggest that atomoxetine may be a safer choice than methylphenidate for the treatment of ADHD when suicidal ideation is a concern. In this regard, monitoring suicidal ideation and behavior along with family education should be considered in all children and adolescents suffering ADHD.

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## Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is the most common childhood neurobehavioral disorder with 3-7% prevalence among school-aged children. It presents with significant problems in attention, excess activity and impulsivity and leads to impairment in child's major life activities (1).

Treatment goal in children with ADHD is to minimize the alteration in their social daily behavior and function. Pharmacotherapy is the principal treatment for ADHD (2). Stimulants, principally methylphenidate have been considered as first choice treatment in the treatment of ADHD for a long time. Atomoxetine, a norepinephrine reuptake inhibitor, is the only non-stimulant medication that is approved for the treatment of this disorder (3-5).

Children and adolescents with ADHD have behavioral traits such as impulsivity and aggression, as well as higher risk for having comorbid psychiatric disorders, which make them more prone to suicide. Moreover, associations between the use of methylphenidate or atomoxetine with suicidal ideation and suicide-related behavior at all ages have been reported (0.37% in pediatric patients and 0.11% in adults) (6,7). World Health Organization (WHO) received 189 cases of adverse drug events due to atomoxetine use in 2007. Among those cases, 41 suicidal attempts were reported among children and adolescents out of whom 29 regained their health without any further adverse events and one died (6,8).

The present study was designed to compare the effects of atomoxetine and methylphenidate on suicidal thoughts and behavior in children and adolescents.

## Methods

This observational, cross sectional study with convenience sampling method compares the suicidal ideation among children and adolescents with ADHD who have been receiving either atomoxetine or methylphenidate. Tehran University of Medical Sciences ethics committee approved the study. All patients entered the study with informed consents of either their parents or their guardians.

A total of 57 patients recruited from the children and adolescent psychiatry clinic at Roozbeh Hospital and Children Medical Center, as well as a private psychiatric office. About half of the eligible participants, refused to fill out the questionnaire, probably due to cultural issues about the suicide and stigma around the subject.

Children and adolescents between 7 to 17 years of age with the diagnosis of ADHD based on DSM-5 criteria, and those who had been on either atomoxetine or methylphenidate for at least 12 months prior to entering the study were involved. All the diagnoses were made by a child psychiatrist with an interview with the patient and a family member. Exclusion criteria included history of any kind of malignancy, cardiovascular disorders, diabetes, endocrine disorders and mental retardation, taking any other prescribed medications at the time of study, pregnancy and breastfeeding.

A Farsi version of Positive and Negative Suicide Ideation (PANSI) inventory was applied for the assessment.

The inventory was originally developed by Osman and his colleagues in 1998 and is a self-report inventory with 14 items assessing both positive and negative factors affecting suicidal ideation on a five-point Likert scale. Each item rates from 1 (never) to 5 (most of the time). The time refers to the past two weeks, including the day the questions are asked. PANSI has two subscales: Positive Suicidal Ideation and Negative Suicidal Ideation with 6 and 8 items respectively.

Negative risk factors, which may increase the risk for suicidal ideation and behavior, include depression, hopelessness, and negative thoughts due to stress-related events. In contrast, positive factors such as connection and good relationship with family members and problem-solving strategies are considered as protective factors against suicide. The consideration of both negative and positive factors by PANSI makes it a very useful tool for the assessment of suicidal ideation (8, 9). Positive scores equal or less than 3.33 and negative scores equal or more than 1.63 are considered as high risk for suicidal ideation (9-11). Abbasi et al., evaluated validity and reliability of the Persian version of PANSI, and reported Cronbach's α coefficient equaled to 0.73 and 0.76 for positive and negative risk factors respectively (12).

All participant filled in the questionnaire and a child psychiatrist was present to clarify any incomprehensible part.

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS) (version 22.0.0.0 2013 IBM Corporation). Differences among age groups, duration of therapy and comparison of positive and negative scores in both genders were analyzed using t-test. In addition, a one-way analysis of variance (ANOVA) was applied to examine the differences in positive and negative scores among different age groups. Moreover, chi-square and Fisher's exact tests were performed to examine the effects of past history of medication use and other present illnesses on suicidal ideation. P-value of $< 0.05$ was considered as significant.

## Results

A total of 57 students (50 boys and 7 girls) between 9 to 16 years of age were enrolled in this study. Patients were third to tenth graders. The demographic characteristics of the patients are shown in Table 1. There was no significant difference between mean age of the both groups (P =0.254). Moreover, duration of the therapy was not significantly different among them (P=0.145).

**Table 1.** Demographic characteristics of the participants.

| medication | Atomoxetine (n = 28) | Methylphenidate (n = 29) |
|---|---|---|
| Age (years)<br>(mean ± SD) | 12.10 ± 1.68 | 11.55 ± 1.93 |
| Gender (n) | Boys 28<br>Girls 0 | Boys 22<br>Girls 7 |
| Level of education mean (years)<br>(mean ± SD) | 5.88 ± 1.64 | 5.42 ± 1.89 |
| Duration of therapy mean (months)<br>(mean ± SD) | 19.92 ± 7.06 | 24.74 ± 15.89 |

Twenty-eight patients have been taking atomoxetine at doses of 10 to 60 mg/day (30.25 ± 18.50 mg/day). Twenty-four out of the 28 subjects had received methylphenidate or risperidone prior to the initiation of the atomoxetine.

Twenty-nine patients were on methylphenidate 7.50-55 mg/day (mean=30.62 ± 10.92 mg/day).

As shown in Table 2, the mean positive and negative scores in atomoxetine group were found to significantly differ from those of methylphenidate group. No risk of suicidal ideation was detected in the atomoxetine group, while in the methylphenidate group 15 out of 29 patients (51.7%) scored above the cutoff point. Negative and positive scores did not differ significantly among boys and girls in the methylphenidate group (P=0.516).

No correlations were found between positive or negative scores and age among patients taking either atomoxetine or methylphenidate (P=0.075).

In terms of the relationship between suicidal ideation and history of other medications prior to the current therapy and other concurrent disorders, chi-square test showed no significant difference in methylphenidate group (P=0.100 and 0.500 respectively). This analysis was not considered in atomoxetine group due to the absence of suicidal ideation.

**Table 2.** Mean PANSI scores in patients taking methylphenidate and atomoxetine.

| | Methylphenidate (mean ± SD) | Atomoxetine (mean ± SD) | p- value |
|---|---|---|---|
| Positive scores | 3.629 ± 0.830 | 4.26 ± 0.080 | 0.001 |
| Negative scores | 1.44 ± 0.595 | 1.022 ± 0.096 | 0.001 |

## Discussion

The present observational, cross-sectional study found higher rate of suicidal ideation among children and adolescents who receives methylphenidate than those receiving atomoxetine.

Detecting a clear relationship between medication use and suicide as an adverse event is difficult due to the complex nature of the disease and comorbidity with psychiatric disorders (e.g. mood disorders, disruptive disorders, etc.) among such patients (12). PANSI has the advantage of assessing both positive and negative risk factors related to suicidal behavior (9,10).

Results of a meta-analysis on 14 systemic double blind reviews among children by Bangs et al., and colleagues in 2008 showed that although suicidal ideation due to atomoxetine use was low (five out of 1357 and one case of suicidal behavior) but its prevalence was significantly higher than placebo (zero out of 851) (8). In contrast, a cohort study by Lindet et al., revealed no significant increase in the risk of suicidal events in youths taking atomoxetine compared with those on stimulants (14). Our different finding might be due to age group differences of participants, as nearly all cases of suicidal ideation in the Bangs et al study occurred in patients less than 12 years of age, similar to the methylphenidate group in our study.

Our data showed that suicidal ideation due to methylphenidate use was significantly higher than atomoxetine use, however, another study reported that methylphenidate use resulted in reduced rate of suicide related events during the treatment periods; no significant increase in suicide rates was noted in patients on atomoxetine or mixed therapy (15).

In a systematic review on atomoxetine safety, data from

2009 through 2011 show that suicide related events in children and adolescents are comparable between atomoxetine and methylphenidate use (16). This result is similar to another meta-analysis on suicidal related events in patients treated with atomoxetine or methylphenidate (17,18).

Bangsand colleagues conducted another meta-analysis on suicidal related behavior or ideation in children treated with atomoxetine where they noted that the available evidence had not shown an increased risk of the aforementioned adverse effect (18). However, this is in contrast with the study of Capuano et al., that presented the data from the Italian ADHD registry where all studied children on atomoxetine (7 cases) had self-harm issues or suicidal ideation (20).

The present study only revealed the prevalence of suicide ideation among patients and one cannot deduce any causal effect relationship between the two variables of medication and suicidal ideation. However, it is worth noting that atomoxetine had been prescribed for patients who either had other comorbidities or were unresponsive to methylphenidate. Hence, the increased risk of suicidal related problems, if any, was expected to be higher among them.

This study suffered two limitations: a small sample size and a high rate of drop-outs. This was due to poor cooperation of the majority of patients and the nature of questions. Even though the authors believe that proper communication skills were applied when visiting patients and their parents or guardians, more than 50% of parents or guardians were not willing to answer all of the questions on PANSI that may partly be due to the cultural view on suicide.

In conclusion, the authors suggest that atomoxetine may be a safer choice than methylphenidate for the treatment of ADHD when suicidal ideation is a concern. Monitoring suicidal ideation and behavior should be considered in all children and adolescents suffering ADHD who are on medications and should be mentioned to parents and clinical staff.

Current study found higher suicidal ideation among children and adolescents with ADHD who have been receiving methylphenidate than those receiving atomoxetine. The authors of this study suggest that atomoxetine may be a safer choice than methylphenidate for the treatment of ADHD when suicidal ideation is a concern. In this regard, monitoring suicidal ideation and behavior along with family education should be considered in all children and adolescents suffering ADHD.

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