

# Preliminary Investigation on Duloxetine Efficacy in the Treatment of Children With Attention-Deficit Hyperactivity Disorder

Nasrin Dodangi,<sup>1</sup> Nastaran Habibi,<sup>1,\*</sup> and Ali Nazeri astaneh<sup>1</sup>

<sup>1</sup>Department of Psychiatry, University of Social Welfare and Rehabilitation Sciences, Tehran, IR Iran

\*Corresponding author: Nastaran Habibi, Department of Psychiatry, University of Social Welfare and Rehabilitation Sciences, Tehran, IR Iran. Tel: +98-2133401604, Fax: +98-2133401604, E-mail: dr\_nhabibi@yahoo.com

Received 2015 April 27; Revised 2015 October 25; Accepted 2015 November 14.

## Abstract

**Background:** Stimulants are first-line agents for the treatment of attention-deficit/hyperactivity disorder (ADHD). Despite the impressive track record of stimulants in the treatment of ADHD, they fail in 25% of patients due to lack of efficacy or the emergence of unwanted side effects.

**Objectives:** In this study, we investigated the efficacy and safety of duloxetine, a serotonin and norepinephrine reuptake inhibitor, in the treatment of children with attention-deficit hyperactivity disorder (ADHD).

**Patients and Methods:** In an open label clinical trial, 13 children aged 6 – 11 years diagnosed with ADHD were prescribed 30 mg/day duloxetine once daily by oral administration for six weeks. Conners Parent Rating Scale-Revised-Short form (CPRS-R-S) and the ADHD Rating Scale were used to assess the efficacy of the treatment.

**Results:** Ten children with a mean age of  $8.40 \pm 1.67$  years terminated the trial. A significant reduction in CPRS-R and its subscales was evident from week four of the study. In terms of side effects, duloxetine was generally safe and well tolerated.

**Conclusions:** This preliminary assessment suggests that duloxetine may be a medication of interest in the treatment of children with ADHD. Further controlled studies with larger samples are required to evaluate the efficacy of duloxetine in treatment of children with ADHD.

**Keywords:** Attention Deficit, Hyperactivity Disorder, Children, Duloxetine

## 1. Background

Attention-deficit hyperactivity disorder (ADHD) is one of the most common childhood disorders characterized by overactivity, impulsivity, and inattentiveness (1).

Pharmacotherapy constitutes the principal part of ADHD treatment. Psychostimulant medications, including methylphenidate and amphetamines, are the first-line therapies for ADHD (2). These agents affect the dopaminergic and noradrenergic systems (3). However, reduced appetite, insomnia, irritability, and dysphoria are among the common adverse effects associated with stimulants. In addition, a controversy exists in their use in ADHD adolescents with or at risk for substance use disorders (2, 4). Therefore, searching for alternative or more effective agents is necessary.

Antidepressant medications have been explored in the treatment of ADHD symptoms, and their benefits are mainly proposed as related to norepinephrine-dopamine agonistic activity (5, 6). Preliminary reports have been presented on the effectiveness of venlafaxine hydrochloride, a serotonin and norepinephrine reuptake in-

hibitor (SNRI) antidepressant, in the treatment of ADHD symptoms in children and adolescents (7, 8).

Duloxetine, an antidepressant agent with an SNRI mechanism, is currently indicated for the treatment of major depressive disorder (MDD) in adults (9, 10). In addition, it has been implicated to be a beneficial treatment for physical pain associated with depression and generalized anxiety disorder in adults (11-14). In child and adolescent psychiatry, preliminary reports have been conducted on the successful use of duloxetine in adolescents with chronic pain and comorbid MDD (15) and childhood depression with pain and dissociative symptoms (16). Moreover, duloxetine has been shown to be generally safe and well tolerated in various controlled trials (17-19). The reported side effects in adult trials include nausea, dry mouth, constipation, fatigue, decreased appetite, somnolence, and hyperhidrosis (9, 20).

## 2. Objectives

In this open-label clinical trial, we investigated the effi-

cacy and safety of duloxetine in the treatment of children with ADHD.

### 3. Patients and Methods

#### 3.1. Participants

The study was conducted at the Akhavan and Rofide child psychiatry clinics at the University of Social Welfare and Rehabilitation Sciences in Tehran, the capital city of Iran. Children aged 6 - 11 years with the diagnosis of ADHD were included. The sample size was calculated according to Cohen's method by power of 80%, alpha of 0.05, and effect size of 0.8. The participants were required to be off any medication at least two weeks prior to the study entry. The exclusion criteria included: (i), comorbidity of pervasive developmental disorder, bipolar disorder, conduct disorder, and psychotic disorder; (ii), a concurrent comorbidity requiring treatment prior to trial entry or during the trial; (iii), clinically significant medical illness requiring pharmacotherapy; (iv), history of hypersensitivity to duloxetine; and (v), mental retardation. The study was conducted from September 2012 until July 2014. It was fulfilled in accordance with the Declaration of Helsinki and approved by the ethics committee of the University of Social Welfare and Rehabilitation Sciences. A written informed consent was obtained from the parents.

#### 3.2. Study Design

This study was an open-label trial for a total duration of six weeks. Duloxetine was orally titrated up starting with 15 mg/day in the first week once daily and 30 mg/day in the next five weeks once daily. The participants were not permitted to receive any other concomitant medication during the trial.

The diagnosis of ADHD based on the Diagnostic and Statistical Manual of Mental Disorder-IV (DSM-IV) criteria and the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime (K-SADS-PL) interview (for the diagnosis of ADHD and comorbidities) was fulfilled for all participants at baseline. K-SADS-PL is a semi-structured interview that enables the interviewer to make judgment during the interview (21). The reliability and the validity of the Persian translation of K-SADS-PL were established in Iranian children before (22, 23). Conners Parent Rating Scale-Revised-Short form (CPRS-R-S) and the ADHD Rating Scale were used to assess the efficacy of the therapy. The self-reported scales Revised Children's Manifest Anxiety Scale (RCMAS) and the Children's Depression Inventory (CDI) were used to assess anxiety and depressive symptoms, respectively. CPRS-R-S and the ADHD Rating Scales are two clinical tools for monitoring the treatment response of ADHD symptoms by parents. CPRS-R-S includes 27 questions of oppositionality, cognitive/inattentive, hyperactivity, and ADHD index subscales

(24, 25). The ADHD Rating Scale includes 18 questions according to the DSM-IV-TR criteria. RCMAS is a 37-item inventory designed to assess the level and the nature of anxiety by evaluating the physiological, apprehensive, worry-oversensitivity, and social concerns- concentration areas of anxiety (26). CDI is a 27-item assessment tool evaluating the emotional, cognitive, and behavioral symptoms of depression in the preceding two weeks. The inventory consists of 14 direct and 13 indirect questions, with an overall minimum score of zero and a maximum score of 54 (27). Children with a total score between 0 and 8 are considered to not have depression. CDI and RCMAS have been translated to Persian and normalized in Iranian children, and they have been shown to have good psychometric properties (28, 29). CPRS-R-S and the ADHD Rating Scale were administered at baseline every two weeks and at the end of week six. RCMAS and CDI were assessed at baseline and at the end of week six. Safety and tolerability of the medication were monitored every two weeks using a side effect checklist (made by the researcher) and through the participants' reported adverse effects. Children's vital signs were monitored every two weeks, and their weight and routine laboratory tests were observed at the beginning and end of the trial. This study was registered in the Iranian Registry of Clinical Trial (Irct ID IRCT2012072210363N1).

#### 3.3. Statistical Analysis

SPSS version 21 was used for data analysis. One-way repeated-measure ANOVA was used for the comparison of the variables that evaluate every two weeks, such as CPRS-R-S and its subscales, and the ADHD Rating Scale. Other variables such as vital signs, weight, laboratory indexes, RCMAS, CDI, CGI-I, and CGI-S were analyzed by paired-sample Student's t-test. Statistical significance was considered as  $P < 0.05$ . Normality of the variable's distribution was tested by the Shapiro-Wilk test. If the SIG value of the Shapiro-Wilk test was greater than 0.05, the data would be normal; if the value was below 0.05, the data would significantly deviate from a normal distribution.

### 4. Results

Thirteen children complied with the study criteria and entered the study, but only 10 participants completed the study. Three participants discontinued the trial, two for noncompliance and one for developing gastrointestinal (GI) adverse drug reaction, such as nausea and abdominal pain. The characteristics of the completers and their comorbidities are shown in Table 1.

The severity of ADHD symptoms was evaluated using CPRS-R-S and the ADHD Rating Scale at the beginning of the trial and then every two weeks. The reduction of the scale and its subscales was then compared. Data analysis showed that the decrease in the overall Conners score and its subscales (except for the inattentiveness subscale) and also the ADHD Rating Scale was significant from the sec-

ond week afterwards. The attention-deficit hyperactivity subscale showed a significant decrease compared with baseline values from the fourth week afterwards (Table 2). The overall reduction in the Conners scale compared with the baseline values in the second, fourth, and sixth weeks was 22%, 33%, and 33%, respectively. If the basis of the therapeutic effect of the drug was considered at 25% reduction at least in the overall Conners scale, this effect would start from the fourth week.

CGAS, CGI-I, and CGI-S were the other general scales used for the evaluation of the drug's efficacy. They were measured at the beginning and end of the trial. These scales were compared with each other, and the changes were significant at week six. Additionally, the participants' anxiety and depression at the beginning and end of the study were measured and compared by RCMAS and CDI tools, respectively. However, their differences were not significant (Table 3).

#### 4.1. Drug Adverse Events

Average weight showed no significant difference at the beginning and end of the study. Changes in blood pressure, pulse, electrocardiography, and laboratory parameters including cell blood count, fasting blood sugar, thyroid function tests, blood urea nitrogen, creatinine, liver function tests, and electrolytes, were not significant.

Apart from one patient who was excluded as he did not tolerate the drug because of severe GI problems, two pa-

tients reported anorexia and one reported mild nausea during the first two weeks. These side effects were resolved through the consumption of the drug in the following weeks, and dose reduction or other interventions were not needed. Generally, this drug was well tolerated in this age group with a dose of 30 mg/day.

**Table 1.** Children's Demographic Characteristics and Prevalence of Comorbidities<sup>a</sup>

	Values <sup>b</sup>
<b>Age (range)</b>	1.6 (7 - 11) ± 8.4
<b>Gender</b>	
Male	8 (80)
Female	2 (20)
<b>Combined subtype</b>	8 (80)
<b>Inattentive subtype</b>	2 (20)
<b>ODD</b>	6 (60)
<b>GAD</b>	2 (20)
<b>OCD</b>	2 (20)
<b>LD</b>	1 (10)
<b>Total</b>	10

<sup>a</sup>Abbreviations: GAD, Generalized Anxiety Disorder; LD, Learning Disability; OCD, Obsessive Compulsive Disorder; ODD, Oppositional Defiant Disorder; SD, Standard Deviation.

<sup>b</sup>Data are presented as mean ± SD or No. (%).

**Table 2.** Efficacy of Treatment According to CPRS-R and the ADHD Rating Scale<sup>a,b</sup>

	Baseline	Week 2	p <sup>a</sup>	Week 4	p <sup>b</sup>	Week 6	p <sup>c</sup>	F	P	Effect Size	95% CI	
											Lower	Upper
<b>ADHD. Index</b>	22.2 ± 1.92	18.4 ± 3	0.007	18 ± 2.24	0	17.6 ± 2.6	0.002	20.07	< 0.001	0.834	3.577	5.622
<b>O.Subscale</b>	10.2 ± 2.77	8.2 ± 2.58	0.034	7.6 ± 1.81	0.025	7.8 ± 2.68	0.016	9.59	0.002	0.706	1.495	3.304
<b>I.Subscale</b>	13.4 ± 3.28	11.2 ± 2.86	0.141	10.2 ± 1.92	0.051	9.4 ± 1.94	0.034	7.39	0.005	0.649	2.092	5.907
<b>H.Subscale</b>	11.4 ± 1.67	9.8 ± 1.30	0.003	8.8 ± 2.28	0.003	8.4 ± 1.81	0.001	33.5	< 0.001	0.893	2.523	3.476
<b>ADHD R.S</b>	14.4 ± 0.89	11.4 ± 2.60	0.04	9.4 ± 2.5	0.012	8.6 ± 2.07	0.004	19.93	< 0.001	0.833	4.337	7.262

<sup>a</sup>Abbreviations: ADHD R.S, ADHD Rating Scale; CI, Confidence Interval; CPRS-R, Conners Parent Rating Scale-Revised; H.Subscale, Subscale of Hyperactivity; I.Subscale, Subscale of Inattentiveness; O.Subscale, Subscale of Oppositionality; p

<sup>b</sup>Data are presented as mean ± SD.

**Table 3.** Changes in CGAS, CGI-S, CGI-I, CDI and RCMAS<sup>a,b</sup>

	Week 0	Week6	P Value	95% CI	
				Lower	Upper
<b>CGAS</b>	3 ± 52	6 ± 65	0.006	-23.823	-3.476
<b>CGI-I<sup>c</sup></b>	0.8 ± 3.6	0.8 ± 2.4	0.004	1.230	2.269
<b>CGI-S</b>	0.5 ± 4.4	0.6 ± 2.6	0.009	0.943	2.256
<b>CDI</b>	1.1 ± 8.6	1.5 ± 8.0	0.208	-1.922	2.222
<b>RCMAS</b>	2.5 ± 8.2	1.3 ± 4.8	0.067	-1.974	1.374

<sup>a</sup>Abbreviations: CDI, Children's Depression Inventory; CGAS, Children's Global Assessment Scale; CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity; CI, Confidence Interval; RCMAS, Revised Children's Manifest Anxiety Scale.

<sup>b</sup>Data are presented as mean ± SD.

<sup>c</sup>This scale was assessed at weeks 2 and 6.

## 5. Discussion

To our knowledge, this trial is the first study investigating the efficacy of duloxetine on ADHD children aged 6–11 years. The results suggest that the drug is well tolerated and has a good effect on ADHD symptoms. This effect is observable from the fourth week of drug administration according to the results of CORS-R and the ADHD rating scale.

Several studies have been conducted on the effects of duloxetine in the treatment of ADHD. The first study that showed the effect of duloxetine on ADHD was a case report administering 60 mg/day duloxetine to a 53-year-old man with a recent diagnosis of ADHD. The results demonstrated a significant reduction in the Conners scale (30). Duloxetine has recently been reported to be useful in reducing ADHD symptoms in a 16-year-old girl with ADHD. Similar to our results, the treatment effect was observed after four weeks (31). In another open trial, duloxetine was given to 13 adolescents with ADHD. A significant reduction in ADHD symptoms measured by CPRS-R was observed from week four (32).

According to this study, duloxetine can reduce attention deficit, hyperactivity and oppositionality in ADHD children. Nevertheless, atomoxetine only treats the symptoms of attention deficit and hyperactivity-impulsivity but not oppositionality (33, 34).

Venlafaxine, a drug with an effect mechanism similar to that of duloxetine, may exacerbate the hyperactivity symptoms of ADHD (35). Therefore, although duloxetine and venlafaxine have similar effect mechanisms, they seem to have different effects on ADHD. As a result, more research is needed in this area.

Duloxetine is an anxiolytic and anti-depressant drug (9). This study assessed the intensity of anxiety and depression symptoms using RCMAS and CDI, respectively. The results showed that the severity of these symptoms did not change during the trial. These findings suggest that the useful effects of duloxetine in reducing ADHD symptoms are independent of its anxiolytic and anti-depressant effects.

One of the objectives of this study was to evaluate the tolerability and safety of duloxetine in the target age group. In this study, we gradually increased the dose of duloxetine to 30 mg/day, so that tolerance would be established against some minor complications developed during the first weeks. The safety profile of duloxetine in our study is consistent with the present published data mentioning GI side effects (36). Therefore, the drug can be concluded to have a tolerable side effect profile. However, studying the long-term effects of the drug in longer-term studies is necessary.

The limitations of this study include its open nature, absence of control group, small sample size, and short-term duration of the trial. Another limitation is that the Conners Teacher Rating Scale was not used in the study.

We suggest that further double-blind comparative studies should be conducted with a larger sample size,

a longer trial, and the administration of higher doses of the drug.

## Acknowledgments

The authors would like to express their gratitude to all the children and their parents who participated in this study.

## Footnotes

**Authors' Contribution:** Design and conduction, Nasrin Dodangi; patients follow up and data collection, Nasrin Dodangi, Nastaran Habibi; data analysis, Ali Nazeri Astaneh; preparation of manuscript, Nasrin Dodangi, Nastaran Habibi, Ali Nazeri Astaneh.

**Funding/Support:** This study was supported by the deputy of research of the University of Social Welfare and Rehabilitation Sciences.

## References

1. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 5th ed. Arlington: American Psychiatric Publishing; 2013. pp. 466–71.
2. Murray DW, Arnold LE, Swanson J, Wells K, Burns K, Jensen P, et al. A clinical review of outcomes of the multimodal treatment study of children with attention-deficit/hyperactivity disorder (MTA). *Curr Psychiatry Rep*. 2008;**10**(5):424–31. [PubMed: 18803917]
3. Sadock BJ, Sadock VA. *Kaplan and Sadock's comprehensive textbook of psychiatry*. 8th ed. New York: Lippincott Williams and Wilkins; 2005.
4. Leonard BE, McCartan D, White J, King DJ. Methylphenidate: a review of its neuropharmacological, neuropsychological and adverse clinical effects. *Hum Psychopharmacol*. 2004;**19**(3):151–80. doi: 10.1002/hup.579. [PubMed: 15079851]
5. Ratner S, Laor N, Bronstein Y, Weizman A, Toren P. Six-week open-label reboxetine treatment in children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2005;**44**(5):428–33. doi: 10.1097/01.chi.0000155327.30017.8c. [PubMed: 15843764]
6. Garnock-Jones KP, Keating GM. Atomoxetine: a review of its use in attention-deficit hyperactivity disorder in children and adolescents. *Paediatr Drugs*. 2009;**11**(3):203–26. doi: 10.2165/00148581-200911030-00005. [PubMed: 19445548]
7. Findling RL, Greenhill LL, McNamara NK, Demeter CA, Kotler LA, O'Riordan MA, et al. Venlafaxine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2007;**17**(4):433–45. doi: 10.1089/cap.2007.0119. [PubMed: 17822339]
8. Mukaddes NM, Abali O. Venlafaxine in children and adolescents with attention deficit hyperactivity disorder. *Psychiatry Clin Neurosci*. 2004;**58**(1):92–5. [PubMed: 14678464]
9. Green WH. *Child and Adolescent Clinical Psychopharmacology*. New York: Wolters Kluwer; 2007. p. 716.
10. Hudson JI, Wohlreich MM, Kajdasz DK, Mallinckrodt CH, Watkin JG, Martynov OV. Safety and tolerability of duloxetine in the treatment of major depressive disorder: analysis of pooled data from eight placebo-controlled clinical trials. *Hum Psychopharmacol*. 2005;**20**(5):327–41. doi: 10.1002/hup.696. [PubMed: 15912562]
11. Carter NJ, McCormack PL. Duloxetine: a review of its use in the treatment of generalized anxiety disorder. *CNS Drugs*. 2009;**23**(6):523–41. doi: 10.2165/00023210-200923060-00006. [PubMed: 19480470]
12. Gupta S, Nihalani N, Masand P. Duloxetine: review of its pharmacology, and therapeutic use in depression and other psychiatric disorders. *Ann Clin Psychiatry*. 2007;**19**(2):125–32. doi: 10.1080/10401230701333319. [PubMed: 17612852]
13. Khan AY, Macaluso M. Duloxetine for the treatment of gen-

- eralized anxiety disorder: a review. *Neuropsychiatr Dis Treat*. 2009;**5**:23-31. [PubMed: 19557096]
14. Prakash A, Lobo E, Kratochvil CJ, Tamura RN, Pangallo BA, Bullok KE, et al. An open-label safety and pharmacokinetics study of duloxetine in pediatric patients with major depression. *J Child Adolesc Psychopharmacol*. 2012;**22**(1):48-55. doi:10.1089/cap.2011.0072. [PubMed: 22251023]
  15. Meighen KG. Duloxetine treatment of pediatric chronic pain and co-morbid major depressive disorder. *J Child Adolesc Psychopharmacol*. 2007;**17**(1):121-7. doi: 10.1089/cap.2006.0042. [PubMed: 17343560]
  16. Desarkar P, Das A, Sinha VK. Duloxetine for childhood depression with pain and dissociative symptoms. *Eur Child Adolesc Psychiatry*. 2006;**15**(8):496-9. doi: 10.1007/s00787-006-0553-4. [PubMed: 16732464]
  17. Wernicke JF, Gahimer J, Yalcin I, Wulster-Radcliffe M, Viktrup L. Safety and adverse event profile of duloxetine. *Expert Opin Drug Saf*. 2005;**4**(6):987-93. doi: 10.1517/14740338.4.6.987. [PubMed: 16255658]
  18. Wernicke J, Lledo A, Raskin J, Kajdasz DK, Wang F. An evaluation of the cardiovascular safety profile of duloxetine: findings from 42 placebo-controlled studies. *Drug Saf*. 2007;**30**(5):437-55. [PubMed: 17472422]
  19. Zhang L, Chappell J, Gonzales CR, Small D, Knadler MP, Callaghan JT, et al. QT effects of duloxetine at supratherapeutic doses: a placebo and positive controlled study. *J Cardiovasc Pharmacol*. 2007;**49**(3):146-53. doi: 10.1097/FJC.0b013e318030aff7. [PubMed: 17414226]
  20. Gahimer J, Wernicke J, Yalcin I, Ossanna MJ, Wulster-Radcliffe M, Viktrup L. A retrospective pooled analysis of duloxetine safety in 23,983 subjects. *Curr Med Res Opin*. 2007;**23**(1):175-84. doi: 10.1185/030079906X162719. [PubMed: 17257478]
  21. Dulkan MK, Mina K. *Dulkan's Textbook of Child and Adolescent Psychiatry*. Arlington: American Psychiatry Pub; 2010.
  22. Ghanizadeh A, Mohammadi MR, Yazdanshenas A. Psychometric properties of the Farsi translation of the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version. *BMC Psychiatry*. 2006;**6**:10. doi: 10.1186/1471-244X-6-10. [PubMed: 16539703]
  23. Shahrivar Z, Kousha M, Moallemi S, Tehrani-Doost M, Alaghband-Rad J, Shahrivar. The reliability and validity of kiddie-schedule for affective disorders and schizophrenia- present and lifetime. *Child Adolescent Ment Health*. 2010;**15**(2):97-102. doi: 10.1111/j.1475-3588.2008.00518.x.
  24. Conners CK, Barkley RA. Rating scales and checklists for child psychopharmacology. *Psychopharmacol Bull*. 1985;**21**(4):809-43. [PubMed: 4089107]
  25. Conners CK, Sitarenios G, Parker JD, Epstein JN. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. *J Abnorm Child Psychol*. 1998;**26**(4):257-68. [PubMed: 9700518]
  26. Reynolds CR, Richmond BO. What I Think and Feel: a revised measure of Children's Manifest Anxiety. *J Abnorm Child Psychol*. 1997;**25**(1):15-20. [PubMed: 9093896]
  27. Kovacs M. The Children's Depression, Inventory (CDI). *Psychopharmacol Bull*. 1985;**21**(4):995-8. [PubMed: 4089116]
  28. Rajabi G, H, R. An investigation of reliability and validity of child depression inventory in 13 to 15 years old adolescents. *J Psychol Education*. 2007;**37**:23-46.
  29. Taghavi S, M, R. The normalization of revised children manifest anxiety scale (RCMAS) for students in Shiraz. *J Social Sciences Hum Shiraz*. 2006;**22**(4):179-88.
  30. Tourjman SV, Bilodeau M. Improvement with duloxetine in an adult ADHD patient. *J Atten Disord*. 2009;**13**(1):95-6. doi: 10.1177/1087054708326109. [PubMed: 19359667]
  31. Niederhofer H. Duloxetine May Improve Some Symptoms of Attention Deficit/Hyperactivity Disorder, Prim Care Companion. *J Clin Psychiatry*. 2010;**12**(2):e1-e2.
  32. Mahmoudi-Gharaei J, Dodangi N, Tehrani-Doost M, Faghihi T. Duloxetine in the treatment of adolescents with attention deficit/hyperactivity disorder: an open-label study. *Hum Psychopharmacol*. 2011;**26**(2):155-60. doi: 10.1002/hup.1188. [PubMed: 21455975]
  33. Michelson D, Allen AJ, Busner J, Casat C, Dunn D, Kratochvil C, et al. Once-daily atomoxetine treatment for children and adolescents with attention deficit hyperactivity disorder: a randomized, placebo-controlled study. *Am J Psychiatry*. 2002;**159**(11):1896-901. doi: 10.1176/appi.ajp.159.11.1896. [PubMed: 12411225]
  34. Michelson D, Faries D, Wernicke J, Kelsey D, Kendrick K, Sallee FR, et al. Atomoxetine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, dose-response study. *Pediatrics*. 2001;**108**(5):E83. [PubMed: 11694667]
  35. Olvera RL, Pliszka SR, Luh J, Tatum R. An open trial of venlafaxine in the treatment of attention-deficit/hyperactivity disorder in children and adolescents. *J Child Adolesc Psychopharmacol*. 1996;**6**(4):241-50. [PubMed: 9231317]
  36. Detke MJ, Lu Y, Goldstein DJ, Hayes JR, Demitrack MA. Duloxetine, 60 mg once daily, for major depressive disorder: a randomized double-blind placebo-controlled trial. *J Clin Psychiatry*. 2002;**63**(4):308-15. [PubMed: 12000204]