

# Liver Enzymes and Bilirubin Levels During Atomoxetine Treatment in Children and Adolescents

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## ABSTRACT

Liver enzymes and bilirubin levels during atomoxetine treatment in children and adolescents

**Objective:** Atomoxetine is the first non stimulant medication approved by FDA for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The objective of this study was to investigate the changes in the liver enzymes levels associated with one month atomoxetine treatment in children with ADHD.

**Methods:** A retrospective chart review was done to evaluate patients treated with only atomoxetine in Bakırköy Prof. Dr. Mazhar Osman Research and Training Hospital for Psychiatry and Neurological Disease, Child and Adolescent Psychiatry Clinic outpatient unit between September 2010 and December 2010. A total of 62 patients between 6-15 years of age were eligible for the study. Patients' baseline and one month follow-up hepatobiliary function tests including alanine aminotransferase (ALT) and aspartat aminotransferase (AST), gamma glutamyl transferase (GGT), alkaline phosphatase (ALP) and total serum bilirubin levels were noted.

**Results:** No case of jaundice or hepatic failure was seen during the one month treatment period. ALT levels in the first month were significantly lower than baseline. The mean levels of other liver enzymes and bilirubin levels of the patients at the first month were not significantly different than baseline. Clinically nonsignificant elevation of liver enzymes and bilirubin from the defined normal levels were observed in 8 (12.9%) patients.

**Conclusion:** Taking into account the limitations of a retrospective chart review in nonrandomized samples, it appears that atomoxetine treatment in short term does not lead to abnormal liver function changes at therapeutic doses in children and adolescents. Prospective studies are needed to assess liver function tests abnormalities in youth population using atomoxetine.

**Key words:** Atomoxetine, ADHD, liver enzymes, hepatotoxicity

## ÖZET

Atomoksetin tedavisi alan çocuk ve ergenlerde karaciğer enzimleri ve bilirubin düzeyleri

**Amaç:** Atomoksetin, Dikkat Eksikliği Hiperaktivite Bozukluğu (DEHB) tedavisinde FDA tarafından kullanılan onayı alan, stimulan olmayan ilk ajandır. Bu çalışmanın amacı, DEHB'si olan çocuk ve ergenlerde bir aylık atomoksetin kullanımıyla ilişkili olarak karaciğer enzim düzeylerindeki değişikliklerin araştırılmasıdır.

**Yöntem:** Çalışmaya, Bakırköy Ruh ve Sinir Hastalıkları Eğitim ve Araştırma Hastanesi Çocuk ve Ergen Psikiyatri Polikliniğinde, Eylül 2010 ve Aralık 2010 arasında muayene edilen, DEHB tanısı konup atomoksetin başlanan tüm hastalar dahil edilmiştir. Toplamda, 6-15 yaş arası 62 hasta çalışma için uygun bulunmuştur. Dosyalardan geriye yönelik olarak, hastaların tedavi öncesi ve bir aylık takipleri sonrasında alanin aminotransferaz (ALT), aspartat aminotransferaz (AST), gamma glutamyl transferaz (GGT), alkalik fosfataz (ALP) ve total bilirubin seviyesi not edilmiştir.

**Bulgular:** Bir aylık tedavi sırasında karaciğer yetmezliği veya sarılık gelişen hiçbir vakaya rastlanmamıştır. İlk ayda ölçülen ALT değerleri, bazal ALT düzeylerine göre anlamlı olarak düşük bulunmuştur. Birinci ayın sonundaki diğer karaciğer enzim düzey ortalamaları ve bilirubin düzeyleri ile bazal düzeyler arasında anlamlı bir fark bulunmamıştır. Sekiz hastada (%12.9) karaciğer enzimlerinde ve bilirubin düzeyinde, tanımlanan normal değerlere göre klinik olarak önemli olmayan yükselmeler saptanmıştır.

**Sonuç:** Randomize olmayan bir örneklemede geriye dönük dosya taramasının kısıtlılıkları olmakla birlikte, atomoksetin tedavisi kısa dönemde terapötik dozlarda çocuk ve ergenlerde karaciğer fonksiyonlarında bir değişime yol açmıyor gibi görünmektedir. Ancak atomoksetin kullanan genç popülasyonda karaciğer fonksiyon testlerindeki değişimleri ve bu değişimler üzerinde diğer değişkenlerin rolünü inceleyen ileri çalışmalara ihtiyaç vardır.

**Anahtar kelimeler:** Atomoksetin, DEHB, karaciğer enzimleri, hepatotoksitesite

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Date of receipt / Geliş tarihi:  
May 7, 2012 / 7 Mayıs 2012

Date of acceptance / Kabul tarihi:  
June 12, 2012 / 12 Haziran 2012

## INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is the most common psychiatric disorder among children and adolescents. Atomoxetine is the first non stimulant medication that has been FDA approved for the treatment of ADHD. Several placebo-controlled trials showed good efficacy and tolerability of atomoxetine. One or two daily doses are required to reach optimal benefit (1,2).

Atomoxetine was associated with relatively few adverse drug reactions: dyspepsia, nausea, vomiting, fatigue, rash, decreased appetite and weight loss (3). Rare but more severe adverse effects of both stimulants and atomoxetine are possible cardiovascular effects. Both drug classes can increase blood pressure and pulse rate, though mostly on a clinically insignificant level (4,5). Furthermore, atomoxetine has been associated with an increased rate of suicidal ideation among children (6) and recently received a black box warning for increased suicidality in children and adolescents. Because atomoxetine is a relatively new treatment option, it is even more important for children and adolescents treated with this drug that are well-monitored and do receive regular physical check-ups. Studies of safety and effectiveness of atomoxetine conducted on large samples have found no clinically significant abnormalities of liver function tests with treatment. However the labeling of atomoxetine was recently modified in 2004 to include severe liver injury among adverse events, based on recent case reports of hepatotoxicity with atomoxetine (7,8). Atomoxetine may cause clinically significant hepatotoxicity either by metabolic idiosyncrasy or by inducing autoimmune hepatitis (7,8).

Although to date there has been no recommendation for clinicians to do routine monitoring of liver function tests during atomoxetine treatment, it has been recommended that parents and clinicians should be informed of the evidence of liver problems during the treatment with this agent (9). Recently, Erdoğan et al. (10) reported an acute liver failure that is probably associated with atomoxetine. Therefore, it may be argued that the effects of atomoxetine on liver functions

of children and adolescents are currently unclear.

In this study we aimed to investigate the changes in the liver enzyme levels associated with one month of atomoxetine treatment in children and adolescents.

## METHODS

All patients who were referred in Bakırköy Prof. Dr. Mazhar Osman Research and Training Hospital for Psychiatry and Neurological Disease Child and Adolescent Clinic outpatient unit between September 2010 and December 2010, and diagnosed as ADHD according to DSM-IV and started on atomoxetine were included in the study.

In our clinic, we usually measure baseline and follow-up liver function tests if a pharmacotherapeutic agent which is metabolized by liver has been started. Patients were included in this study if patients' hepatobiliary function tests including ALT and AST, GGT, ALP and serum bilirubin levels were measured at baseline and one month follow-up.

Patients using vitamin/mineral supplements and/or herbal remedies, having a history of hepatic disease, having any other active and chronic illness, having a comorbid alcohol or drug abuse, having comorbid psychiatric illness, using other medications beside atomoxetine or who used any drug in the last two weeks before atomoxetine has been started and lacking follow-up information were excluded.

Retrospective chart review was done for 216 patients with a diagnosis of ADHD according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV) criteria (12). The numbers of patients treated with atomoxetine were 84. Patients' age at initial evaluation, gender, weight, medical history were recorded from the charts. Atomoxetine dosage information, symptomatic and/or adverse events reported during the treatment, baseline and one month follow-up liver function tests results were recorded. Twenty-two patients, who used other medications besides atomoxetine, having another chronic illness and lacking baseline and follow-up information were excluded. Finally, 62 patients between 6 and 15 years of age were eligible for the study.

**Table 1: Changes of liver enzyme levels between baseline and first month**

Liver enzymes and total bilirubin	Baseline		1 <sup>st</sup> Month		p value	t
	Mean (U/L)	SD	Mean (U/L)	SD		
AST	25.5	4.97	25.55	5.44	-0.106	0.916
ALT	17.5	5.84	15.7	4.14	2.278	0.027
GGT	13.47	8.99	13.5	11.31	-0.056	0.956
ALP	194.2	57.1	188.3	51.19	1.139	0.260
Bilirubin	0.58	0.23	0.60	0.27	-0.636	0.528

SD: Standard Deviation, t= Student's T test, (ALT; alanine aminotransferase, AST; aspartate aminotransferase, ALP; alkaline phosphatase, GGT; gamma glutamyl transferase)

For this study the following limits were defined as elevations of liver enzymes: for ALT: >35 U/L for females, >40 U/L for males; for AST: >35 U/L for females, >40 U/L for males; for GGT: >39 U/L for females, >66 U/L for males; for ALP: between 1 to 9 years of age, >420 U/L for females and males; between 10 to 11 years of age, >560 U/L for females and males; between 12 to 13 years of age, >420 U/L for females, >495 U/L for males; between 14 to 15 years of age; >230 U/L for females, >515 U/L for males; between 16 to 19 years of age, >130 U/L for females, >260 U/L for males. The following limits were defined as elevations of total bilirubin values: >1.2 mg/dl. Elevations in liver enzymes and bilirubin were accepted as clinically relevant if ALT, AST, GGT and ALP levels increased to two-folds of established reference ranges and if total bilirubin values were greater than normal.

### Statistical Analysis

Statistical Package for the Social Sciences for Windows, Version 15.0 (Chicago, IL., USA) was used for statistical comparisons. To evaluate the changes in liver enzymes and total bilirubin levels between baseline and first month, paired samples t-test applied. Covariance analysis used to evaluate the effects of age, gender and dosage on liver enzymes changes. The significance level was accepted as 0.05.

### RESULTS

Eighty-four patients treated with atomoxetine were identified. Twenty-two patients who used any other drug in addition to atomoxetine or whose hepatobiliary function tests data were missing were excluded from the

**Table 2: Correlations of age and changes of liver enzyme levels between baseline and first month**

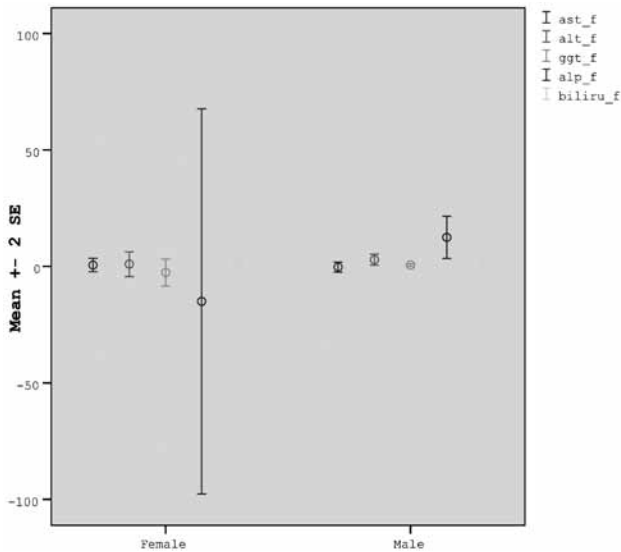
Changes of liver enzymes levels	Age	
	r	p value
AST	-0.03	0.827
ALT	-0.079	0.565
GGT	-0.131	0.434
ALP	0.014	0.918
Bilirubin	0.157	0.287

r= Spearman's rho, (ALT; alanine aminotransferase, AST; aspartate aminotransferase, ALP; alkaline phosphatase, GGT; gamma glutamyl transferase)

study. Sixty two child and adolescent patients treated with atomoxetine were included in the study. The study included 51 (82.3%) male, 11 (17.7%) female, ages between 6 and 15 (mean age 10.07±2.52). The dose of atomoxetine ranged from 10 to 60 mg/day or 0.5 to 1.32 mg/kg/day. Atomoxetine was routinely started with a dose of 0.5 mg per kilogram body weight, with a target dose of 1.2 mg per kilogram body weight after one week.

### Liver Function Tests

No case of jaundice or hepatic failure was seen in the treatment period of one month. ALT levels were significantly lower than baseline at first month. The mean levels of other liver enzymes and bilirubin levels of the patients at the first month were not significantly different than baseline. Mean levels of total bilirubin was 0.58 mg/dl at baseline and 0.60 mg/dl at first month. Comparison of liver enzymes at the baseline and first month were presented in Table 1. Clinically nonsignificant elevation of liver enzymes and bilirubin from the defined normal levels was observed in 8 different patients. The elevation of AST above the normal range was seen in 1 (0.62%), increase of GGT in 3 (1.86%), increase of total bilirubin was seen in 4



**Graphic 1: Standart mean and values of changes of liver enzyme levels in male and female patients**

(ast; aspartate aminotransferase, alt; alanine aminotransferase, ggt; gamma glutamyl transferase, alp; alkaline phosphatase, biliruru; bilirubin)

(2.48%) patients. No variables (age, gender, dosage) predicted change between those two end-points (Table 2 and Graphic 1).

## DISCUSSION

In this study, we retrospectively evaluated the changes of liver enzymes and serum bilirubin levels with one month of atomoxetine treatment in sixty-two children and adolescents with ADHD. In 8 patients elevation of liver enzymes and bilirubin levels was observed, but this was found as clinically nonsignificant. Interestingly ALT levels were significantly lower than baseline at first month. The variables that might have caused this change were not investigated because of the retrospective design of the study. But it was considered to be a possible feature specific to this study group.

Our results are consistent with previous studies that reported no significant changes of liver enzymes and bilirubin levels with atomoxetine treatment on children and adolescents (13-15). Takahashi et al. (13) assessed efficacy and safety of atomoxetine in 245 Japanese children and adolescents over 8 weeks. They did not

find clinically meaningful treatment differences in laboratory values including liver enzymes between atomoxetine and placebo used patients. Similarly Svanborg et al. (14) studied the safety of atomoxetine in Swedish children and adolescents, over 10 weeks and did not find clinically meaningful treatment differences in laboratory values. Wilens et al. (15) evaluated the efficacy and tolerability of atomoxetine in 617 children and adolescents with ADHD. They did not find clinically meaningful treatment differences in adverse event rates, vital signs, laboratory values including liver enzymes between atomoxetine and placebo used patients. In a meta-analysis (13-study; seven double-blind/placebo-controlled, six open-label), Kratochvil et al. (16) evaluated the effectiveness and tolerability of long-term atomoxetine treatment among young children with ADHD. They concluded that no changes were deemed both statistically significant and clinically meaningful among any vital signs, electrocardiographic measures, or laboratory tests including liver enzymes.

However in literature, there have been reports of hepatic abnormalities with atomoxetine. In an investigation of case reports identified by a computerized search that contained potential hepatic events, of the 7962 pediatric and adult patients treated with atomoxetine in clinical trials, 41 were identified as requiring further analysis. Of those 41 cases, none progressed to liver failure, and most of these events were mild increases in ALT and AST levels (17). During the 4 years after the market launch of atomoxetine, 351 cases of liver injury were related to the drug treatment for ADHD. Of those 351 cases, 69 had explanations unrelated to the use of the drug, 146 presented insufficient information to assess the cause, 133 contained confounding factors and were labeled as possibly related to drug use, and the remaining 3 cases reported liver injury probably related to atomoxetine use (17). Lim et al. (7) reported two children presented with acute hepatitis in the first month of treatment with atomoxetine. Later Stojanovski et al. (8) reported hepatotoxicity in a child treated with atomoxetine. According to these case reports atomoxetine may have a considerable potential to cause liver function

abnormalities. In accordance with these cases the labeling of atomoxetine was recently modified (late 2004) to include severe liver injury among adverse events, based on mentioned case reports of hepatotoxicity with atomoxetine (7,8).

In reported cases, reasons showed for significant hepatotoxicity with atomoxetine were metabolic idiosyncrasy or autoimmune hepatitis induction (7,8). Idiosyncratic drug-induced liver injury (DILI) is unpredictable and does not depend directly on dose. Although some drugs cause DILI through direct damage to hepatocytes or interference with bile secretion, others cause delayed, often idiosyncratic DILI with clinical features, such as mild lymphocytic infiltrate, that are reminiscent of allergic reactions involving activation of the adaptive immune system. Idiosyncratic DILI is rare even among individuals who are exposed to drugs that are known to be hepatotoxic. It occurs in 1 in 5000 to 1 in 100,000 individuals who take medication; the risk is lower for some drugs (18). Pharmacovigilance and pharmacoepidemiology studies in children are infrequent for all drugs. Although in the present study no variables (age, gender, dosage) predicted change between baseline and follow-up values, susceptibility to drug toxicity changes with age and can differ largely between newborns, toddlers, adolescents and adults, because of age-dependent maturation of pharmacokinetic processes. This is

particularly so for the liver which is the main organism for drug metabolism. Most drugs are metabolized through the cytochrome P450 (CYP 450) isoenzymes. The change in maturation and activity of CYP 450 occurring with age may have a strong influence on the capacity to eliminate drugs (19).

This study has a number of limitations. Firstly this study was limited in power by the number of patients and retrospective design. Another limitation of this study is that we did not collect information about patients' prior exposure to atomoxetine or other medications before the washout period. However, to ameliorate this limitation, we included only patients who have normal baseline liver function tests in the study. Further studies are needed with larger randomized samples in prospective design to allow more reliable conclusions.

## CONCLUSION

In conclusion, it appears that atomoxetine treatment in the short term commonly does not lead to clinically significant liver function changes at therapeutic doses in children and adolescents. However based on the reported hepatotoxicity cases, further studies are needed to assess the liver function tests abnormalities and role of variables over these abnormalities in youth population.

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