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# Is atomoxetine effective in some comorbid mental disorders in ADHD? Je atomoxetín účinný na vybrané komorbídne psychické poruchy pri ADHD?

Original research article

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**Abstract** Attention-Deficit/Hyperactivity Disorder (ADHD) is connected with high level of psychiatric comorbidity in paediatric population. Depressive disorder is common comorbid disorder co-existing with ADHD. Atomoxetine is worldwide approved for treatment of ADHD in paediatric population; in addition atomoxetine is effective and safe in treatment of some comorbid disorders in ADHD. Pharmacotherapy of depression is limited and residual symptoms are common. Fluoxetine is currently considered to be the gold standard of treatment of depression, but effectiveness of acute phase of treatment is not sufficient. Atomoxetine as a selective noradrenaline reuptake inhibitor or olanzapine as a multi receptors antagonist drug in combination with fluoxetine could be perspective augmented treatment strategy of depression just for their antidepressant effect. The aim of our following study is to evaluate and compare effectiveness and safety of monotherapy and combined/augmented therapy in acute phase of depression treatment in adolescence, as well as introduce complex modern research methodology of effectiveness and safety of treatment.

**Slovak abstract** Hyperkinetická porucha (ADHD) je chronické neurovývinové ochorenie s najvyššou prevalenciou v detskom a adolescentnom veku, často spojené s vysokou psychiatrickou komrbiditou. V efektívnej a bezpečnej farmakoterapii ADHD sa v pediatrickej populácií celosvetovo uplatňujú psychostimulanciá a atomoxetín. Atomoxetín v kombinácii s fluoxetínom by mohol predstavovať perspektívnu augmentačnú stratégiu v liečbe depresívnej poruchy, a to práve pre jeho noradrenergnú neurotransmisiu a antidepresívny efekt.

**Keywords** *ADHD – Atomoxetine – Depressive disorder – Fluoxetine*

**Kľúčové slová:** *ADHD – atomoxetín – depresia – fluoxetín*

## INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders characterised by core symptoms of inappropriate inattention, hyperactivity and/or impulsivity that can result in multiple negative consequences for the individual's life (APA, 2000). Prevalence rates of ADHD in non-Western countries (e.g. Central Europe and East Asia) range from 7.5% to 12% amongst school-aged children and adolescents (Hong et al., 2014). Aetiology of ADHD is multifactorial with substantial genetic and neurochemical component (Barton, 2005, Kennard et al., 2014). Both genetic and social factors influence the occurrence, duration and severity of ADHD and the comorbidity of variety of psychiatric disorders. Chronic, complex and multidisciplinary treatment is necessary in patients with ADHD (Ondrejka, 2007). The most common comorbid disorders in ADHD are depression and anxiety disorder (Weiping et al., 2015). Selective serotonin reuptake inhibitors (SSRIs) are the first-line treatment for major depressive disorder (MDD) in children psychiatry, primarily fluoxetine in dose 10–20 mg per day, but the effectiveness in acute phase of treatment is not sufficient and more effective augmented treatment strategies are needed (Emslie et al., 2002; Kennard et al., 2014). Atomoxetine is a widely approved, effective and safe non-stimulant drug primarily used for treating ADHD and co-existing disorders,

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mostly MDD. It is a selective inhibitor of the presynaptic noradrenaline transporter. Atomoxetine medication leads to increased noradrenergic neurotransmission and has antidepressant effect (Bangs et al., 2007). Another possibility of more effective/augmented therapeutic strategy is olanzapine as an atypical antipsychotic and multi-receptors antagonist drug with antidepressant effect. The objective of this study is to evaluate the effectiveness and safety of fluoxetine monotherapy in comparison with combined/augmented therapy (fluoxetine + olanzapine, fluoxetine + atomoxetine) in acute 6-week treatment of depression in adolescence.

## METHODS AND MATERIALS

The aim of the study is to evaluate the dynamics of depression symptoms in time, executive functions, some psychological spiritual signs and selected markers of autonomic nervous system (ANS) describing cardiovascular autonomic dysfunction and the incidence of side effects amongst three therapeutic strategies (monotherapy vs. combined augmented therapy).

The inclusion criteria consist of comorbid disorders in ADHD – depressive episode (F32)/recurrent depressive episode (F33), inpatients in Clinic of Psychiatry in Martin, adolescent of age ranging from 15 to 18 years, ability to participate in research. The exclusion criteria consist of cognitive deficit or serious symptomatic disorder.

About 90 inpatients are randomised into three therapeutic lines – fluoxetine monotherapy, combined fluoxetine/atomoxetine therapy and combined fluoxetine/olanzapine therapy. Dynamics of depression symptoms are evaluated by using scales such as subjective CDI (Children Depression Inventory) and objective CDRS-R (Children Depression Rating Scale-Revised) and MADRS (Montgomery and Asberg Depression Rating Scale). The clinical impression is evaluated by CGI (Clinical Global Impression); psychological spiritual signs by questionnaires such as The Life Meaningfulness Scale Halama, Snyder Hope Scale, UCLA Loneliness Scale and Loneliness Questionnaire and Emotional habitual subjective well-being scales SEHW; risk of suicidality by C-SSRS (Columbia Suicide Severity Rating Scale); and safety/tolerability of the treatment by UKU Scale (The Udvalg for Kliniske Undersogelser Side Effect Rating Scale). Executive functions are measured subjectively by computer psychodiagnostic test and objectively by questionnaire Brief for parents (Behaviour Rating Inventory of Executive Function). Variations in parameters of ANS, such as heart rate variability, pupillary response and galvanic skin response, are measured by Varcore, Pupillometry and the others. Before, during and after the acute 6 - week phase of treatment, clinical (blood pressure and heart rate) and anthropometric parameters (weight and body mass index) are monitored, laboratory tests (biochemical, hematologic and coagulation parameters) are analysed and the ECG obtained is focused on the QTc interval predicting the risk of arrhythmia is realized.

The study was approved by an ethics committee. Patients who have not signed an informed consent can't enter the study. All gained data will be used only for scientific purposes. Personal data will not be published.

## DISCUSSION

The high level of comorbid disorders have been found in ADHD, including mood and anxiety disorder as well as other mental disorders, such as substance use disorders. Comorbid disorders often affect research and clinical practice and have influence on diagnosis, prognosis and treatment of disorders. ADHD and oppositional defiant disorder (ODD) are the most common children disorders and frequently co-occur (Šnircová et al., 2013). Moreover, there is a growing evidence of comorbidities between ADHD and affective disorders, especially depression. The baseline rate of major depression in children diagnosed with ADHD was approximately 30% (Biederman, 1996). Children with both ADHD and depression were discovered to have a high risk of psychosocial impairments with negative results. According to one study, amongst the 135 children with ADHD, 27% had a comorbid anxiety disorder, 18% had a comorbid depressive disorder and another 15% had both comorbid anxiety and depressive disorders (Weiping et al., 2015).

MDD is a relatively common and serious disorder that affects up to 2% of children and 8% of adolescents connected with poor social functioning. Adolescent depression is associated with negative academic, social and health outcomes, including depression in adulthood, increased risk of suicidal behaviour and substance abuse. Suicidal attempts occurred in 48% of individuals with depression onset in childhood or adolescence compared with 26% in adulthood (DeFilippis & Wagner, 2014). Widely approved, safe and well-tolerated medication used for MDD is fluoxetine. There are many studies that describe the improvement of depression symptoms during acute phase of treatment. The effectiveness of fluoxetine was confirmed in three randomised controlled trial studies in children and adolescents with MDD (Emslie et al., 1997; Emslie et al., 2002; March et al., 2004). According to Emslie et al. (2002), fluoxetine in dose 20 mg daily was associated with greater mean improvement in CDRS-R score than placebo after 1 week ($p < 0.05$). In a randomised, double-blind, placebo-controlled trial of fluoxetine in children and adolescents with depression, fluoxetine was superior to placebo in the acute-phase treatment of depression in child and adolescent outpatients with severe, persistent depression. Complete remission of symptoms was rare (Emslie et al., 1997). In the study by Emslie et al. (2008) that compared fluoxetine and placebo in continuation treatment to prevent relapse of MDD in children and adolescents, 42.0% in the fluoxetine group relapsed, compared with 69.2% in the placebo group. Continuation treatment after acute phase of treatment with fluoxetine was superior to placebo in preventing relapse and in increasing time to relapse in

patients with MDD. According to several studies, only 30% children have remitted after acute treatment of MDD and residual symptoms are often common (Kennard et al., 2014). More effective therapeutic strategies are needed.

Olanzapine as a multi-receptors antagonist shows antidepressant effect. According to Detke et al. (2015), olanzapine/fluoxetine combination (OFC) therapy was superior to placebo, mean change in CDRS-R total score was greater for OFC-treated patients than for placebo-treated patients. Rates of and times to response and remission were statistically significantly greater for OFC than for placebo-treated patients. Some adverse effects, such as weight gain, hyperlipidaemia, increased appetite and somnolence, were observed. But the benefits should be weighed against the risk of adverse events.

Atomoxetine medication for its antidepressant effect suggests effective therapeutic strategy in comorbid MDD in combination with fluoxetine. Atomoxetine is approved for the treatment of ADHD in paediatric population. Atomoxetine repeatedly showed comparable efficacy in treatment of core symptoms of ADHD in several studies (Šnircová et al., 2013). In addition, atomoxetine is effective and safe in treatment of some comorbid disorders in ADHD, especially affective disorders. Atomoxetine was originally named tomoxetine, with initial research of the treatment of major depression (Zerbe et al., 1985). Phase III trials were completed and initial data suggested it as a potentially effective treatment for depressive disorder. However, development of the drug for the treatment of depression was discontinued in 1990 for unknown reasons. In 1996, the medication was re-presented as a potential treatment for ADHD. The medication was renamed atomoxetine to avoid confusion with the cancer drug tamoxifen (Ledbetter, 2006).

Only a few studies on the effectiveness of using atomoxetine in treating comorbid depression symptoms in patients with ADHD are available. According to the study of Bangs et al. (2007), atomoxetine was considered to be an effective and safe treatment for ADHD in adolescents with ADHD and comorbid MDD. Atomoxetine treatment was associated with significantly more nausea and decreased appetite. According to the study of Kratochvil et al. (2005) in paediatric patients with ADHD and comorbid symptoms of depression or anxiety, atomoxetine monotherapy appears to be effective for treating ADHD. Patients were randomised to treatment with fluoxetine or placebo under double-blind conditions for 8 weeks with atomoxetine. Anxiety, depression and ADHD symptoms were reduced. Combined atomoxetine/fluoxetine therapy was well tolerated. The combination group had higher increases in blood pressure and pulse.

Combined/augmented therapeutic strategies (atomoxetine + fluoxetine and olanzapine + fluoxetine) are limited, not enough examined, and more research strategies are needed. Complex, modern and interdisciplinary methodology of our research predicts novel and previously unknown information about the effectiveness of treatment of depression as a comorbid disorder in ADHD. For example, variations in parameters of ANS offer new information about the safety of treatment. Some psychological spiritual signs such as meaningfulness, hope and loneliness do not contain diagnostic criteria for depression, but these signs are significant in depression and have a high influence on depression treatment.

## CONCLUSION

Atomoxetine as a non-stimulant drug with antidepressant effect is considered to be effective in some comorbid disorders in ADHD, such as depression. Fluoxetine monotherapy in treatment of MDD is safe and well tolerated, but not enough effective after acute phase of treatment in patients with depression. Residual symptoms are common, and relapse/recurrence of depression is typical for 40–70% of adolescent patients. More effective therapeutic strategies are limited and also necessary. Combined/augmented therapeutic strategies suggest higher level of treatment effectiveness, better response to treatment, shorter time to remission and relapse prevention in patients with MDD. Combined fluoxetine/atomoxetine or fluoxetine/olanzapine therapy is predicted to be more useful when compared with fluoxetine monotherapy in patients with MDD. Combined/augmented treatment in comorbid depression in ADHD is needed, and more research is necessary.

*References*


[1] American Psychiatric Association (APA). Disorders usually first diagnosed in infancy, childhood, or adolescence. Diagnostic and statistical manual of mental disorders, 4th edn, text revision. Washington, DC: American Psychiatric Association. 2000.

[2] Bangs ME, Graham JE, Thomas JS et al.: Efficacy and safety of atomoxetine in adolescents with attention-deficit/hyperactivity disorder and major depression. J Child Adolesc Psychopharmacol. 2007;17(4):407–420.

[3] Barton, J. Atomoxetine: a new pharmacotherapeutic approach in the management of attention deficit/hyperactivity disorder. Arch Dis Child. 2005;90(suppl. L):126–129.

[4] Biederman J, Faraone S, Milberger S et al. A prospective 4-year follow-up study of attention deficit hyperactivity and related disorders. Arch Gen Psychiatry. 1996;53:437–446.

[5] DeFillipis M, Wagner KD. Management of Treatment-Resistant Depression in Children and Adolescents. Pediatr Drugs. 2014;16:353–361.

[6] Detke HC, DelBello MP, Landry J, Usher RW. Olanzapine/Fluoxetine combination in children and adolescents with bipolar I depression: a randomized, double-blind, placebo-controlled trial. J Am Acad Child Adolesc Psychiatry. 2015;54(3):217–224.

[7] Emslie GJ, Heiligenstein JH, Wagner KD et al. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. J Am Acad Child Adolesc Psychiatry. 2002;41(10):1205–1215.

[8] Emslie GJ, Rush AJ, Weinberg WA et al. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. Arch Gen Psychiatry 1997;54(11):1031–1037.

[9] Emslie GJ, Kennard BD, Mayes TL et al. Fluoxetine versus placebo in preventing relapse of major depression in children and adolescents. Am J Psychiatry. 2008;165(4):459–467.

[10] Heiligenstein JH1, Hoog SL, Wagner KD et al. Fluoxetine 40-60 mg versus fluoxetine 20 mg in the treatment of children and adolescents with a less-than-complete response to nine-week treatment with fluoxetine 10-20 mg: a pilot study. J Child Adolesc Psychopharmacol. 2006;16(1-2):207–217.

[11] Hong JH, Novick D, Treuer T et al. Patient characteristics associated with treatment initiation among paediatric patients with Attention-Deficit/Hyperactivity Disorder symptoms in a naturalistic setting in Central Europe and East Asia. BMC Psychiatry. 2014;14:304.

[12] Kennard BD, Emslie GJ, Mayes TL et al. Sequential treatment with fluoxetine and relapse prevention CBT to improve outcomes in pediatric depression. Am J Psychiatry. 2014;171(10).

[13] Kratochvil CJ, Newcorn JH, Arnold LE, et al. Atomoxetine alone or combined with fluoxetine for treating ADHD with comorbid depressive or anxiety symptoms. J Am Acad Child Adolesc Psychiatry. 2005;44(9):915–924.

[14] Ledbetter M. Atomoxetine: a novel treatment for child and adult ADHD. Neuropsychiatr Dis Treat. 2006; 2(4):455–466.

[15] March J, Silva S, Petrycki S et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. JAMA. 2004;292(7):807–820.

[16] Ondrejka I. Hyperkineticka porucha v detskom veku. Cesko-slovenska pediatria. 2007; 6:406–414.

[17] Snircova E, Kulhan T, Ondrejka I, Nosalova G. Atomoxetine as treatment in comorbidity of ADHD. Pokroky vo farmakologii v Slovenskej republike. 2013;8:105–109.

[18] Weiping X, Lixiao S, Jinsong Z. Comorbid anxiety and depression in school-aged children with attention deficit hyperactivity disorder (ADHD) and self reported symptoms of ADHD, anxiety, and depression among parents of school-aged children with and without ADHD. Shanghai Arch Psychiatry. 2015; 25; 27(6):356–367.

[19] Zerbe RL, Rowe H, Enas CG et al. Clinical pharmacology of tomoxetine, a potential antidepressant. J Pharmacol Exp Ther. 1985;232:139–143.