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# Pharmacotherapy of adolescent depression - fluoxetine monotherapy or combined treatment?
# Farmakoterapia adolescentnej depresie - monoterapia fluoxetínom alebo kombinovaná liečba?

Original Paper

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**Abstract** Depressive disorder is one of the most common and serious psychiatric diagnosis in paediatric population, often connected with suicidal risk. In recent years, fluoxetine monotherapy is the gold standard in acute phase of depression treatment in children and adolescents, but is not effective enough after an acute phase of treatment. More helpful researches concerning more effective therapeutic strategies of depression in this age are insufficient. The aim of our study is to evaluate the effectiveness and safety of fluoxetine monotherapy in comparison with combined olanzapine/fluoxetine therapy in acute 6-week treatment of depression in adolescence. We found that combined therapeutic strategy, using olanzapine augmentation is predicted to be more useful in the treatment of adolescent depression.

**Slovak abstract** Depresívna porucha patrí medzi závažné a často sa vyskytujúce ochorenie v pedopsychiatrii, často spojené so suicidálnym rizikom. V súčasnosti je zlatým štandardom akútnej fázy liečby ochorenia fluoxetín, avšak jeho efektivita po akútnej fáze liečby ochorenia nie je dostatočná. Výsledky doterajšieho výskumu týkajúce sa efektívnejšej farmakoterapie depresívnej poruchy u adolescentov sú nedostatočné. Cieľom nášho výskumu bolo posúdiť účinnosť a bezpečnosť monoterapie fluoxetínom a kombinovanej terapie fluoxetín/olanzapín v 6-týždňovej akútnej fáze liečby depresívnej poruchy u adolescentov. Zistili sme, že kombinovaná liečba za použitia augmentácie olanzapínom predstavuje efektívnejšiu terapeutickú stratégiu v liečbe adolescentnej depresie.

**Keywords** *Depression – fluoxetine – olanzapine – adolescence*

**Kľúčové slová:** *Depresia – fluoxetín – olanzapín – adolescencia*

## INTRODUCTION

Major depressive disorder (MDD) in children and adolescents is a common and recurrent disorder, occurring approximately in 2% of children, 4-8% of adolescents and is twice as prevalent in adolescent girls than in boys (Emslie et al., 2002), typically increasing in prevalence (APA, 2013). Adolescent depression is associated with negative academic, social and health outcomes, including depression in adulthood, increased suicidal risk, substance abuse, significant morbidity and suicidality. Depression presents a great burden to individuals with reduction of overall functioning and affects various psychological variables such as the meaningfulness of life and hope (Farsky et al., 2012). Selective serotonin reuptake inhibitors (SSRIs) are the first-line treatment for depression in children and adolescents (Ondrejka, 2016). Fluoxetine in dosage of 20 mg/day is the only SSRI antidepressant approved by the U.S. Food and Drug Administration (FDA) in paediatric population from 8 to 18 years of age (FDA, 2015). Fluoxetine monotherapy is safe and well-tolerated and has shown efficacy in a number of open-label and double-blind, placebo-controlled trials, but only during acute several weeks' treatment (Heiligenstein et al., 2006). The usefulness of fluoxetine monotherapy is limited by not having enough effectiveness after the acute phase of treatment (Kennard et al., 2006). For this reason, recent interest has focused on the new

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therapeutic strategies consisting of combined or augmented therapeutic options, using, for example, antipsychotic drugs. Olanzapine as a multi-receptor antagonist shows antidepressant effect, especially in psychotic and bipolar depression (Detke et al., 2014). Our results showed that fluoxetine/olanzapine combined therapy is effective in the treatment of unipolar and non-psychotic depression.

## MATERIAL AND METHODS

The study sample was composed of 40 adolescent inpatients in Clinic of Psychiatry, University Hospital, Martin (aged 15-17 years, 16.2 ± 1). Inclusion criteria were patients with MDD, who met DSM-5 criteria for non-psychotic MDD and had a CDRS-R total score of > 40 and CGI-S (Clinical Global Impression – Severity) rating of ≥ 4 at study entry and were able to participate in the research. The exclusion criterion was serious symptomatic disease. Study participants were randomized into two lines (20 patients in each line), fluoxetine monotherapy (FXT) and therapy of olanzapine/fluoxetine combination (OFC) for acute 6 weeks phase of treatment of MDD. Fluoxetine was supplied in dosage 20 mg/day and olanzapine in dosage 2.5-5 mg/day according to the patient´s weight. Participants were assessed at baseline, and every week of the 6-weeks treatment (6th week was the end of the acute treatment) using the scales typical for children during the acute phase of treatment. Depressive symptoms were assessed using the CDRS-R (Children´s Depression Rating Scale-Revised); it is a 17-item clinician-rated measure of depression severity and was completed by a clinician at baseline, and every week of 6-weeks' treatment. Clinician´s impression of improvement was evaluated by the CGI-I (Clinical Global Impression Scale Improvement) and was completed every week of 6-weeks' treatment. Adverse effects of the treatment were observed. Data were evaluated by statistical analysis (Pairwise Two-Sided Multiple Comparison Analysis, Dwass, Steel and Critchlow-Fligner Method). The study corresponds with the ethical standards of current scientific research. All collected data are used only for scientific purposes and personal data are not published.

## RESULTS

Both fluoxetine monotherapy (FXT) and olanzapine/fluoxetine combined therapy (OFC) were associated with significant mean improvement in CDRS-R total score after 6-weeks' acute phase of treatment, but the mean improvement was greater in the combined therapy (OFC 59.1 ± 7.9, $p < 0.0001$ vs. FXT 58.1 ± 11.5, $p = 0.0002$). Combined therapy has shown significantly greater reduction of depressive symptoms after the 2nd week of treatment in OFC line ($p < 0.0001$) (Figure 1.a, Table 1.). Combined therapy led to a greater clinical improvement in CGI-I total score as compared with fluoxetine monotherapy after 6-weeks' acute phase of treatment (FXT 3.3 ± 1 vs. OFC 3.1 ± 1.6, $p = 0.03$), clinical improvement was significantly

*Table 1. Changes in CGI-I and CDRS-R total score: at baseline and after 6-week of treatment of MDD (FXT - fluoxetine, OLA - olanzapine)*

| | | FXT group | FXT/OLA group |
|---|---|---|---|
| **CDRS-R scale** | baseline | 58.1±11.5 | 59.1±7.9 |
| | 6-th week | 35.8±12.7 | 33.8±11.3 |
| **CGI-I scale** | 1-st week | 3.9±0.2 | 4.0 |
| | 6-th week | 3.2±1 | 3.1±1.6 |

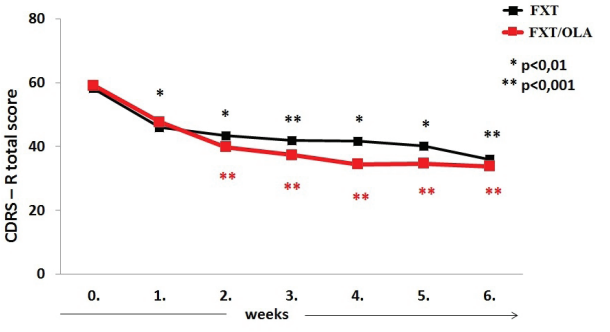


*Figure 1. a) Dynamics of depressive symptoms during 6-weeks' treatment of MDD according to CDRS-R objective scale (FXT - fluoxetine monotherapy group, FXT/OLA - fluoxetine/olanzapine combined therapy).*

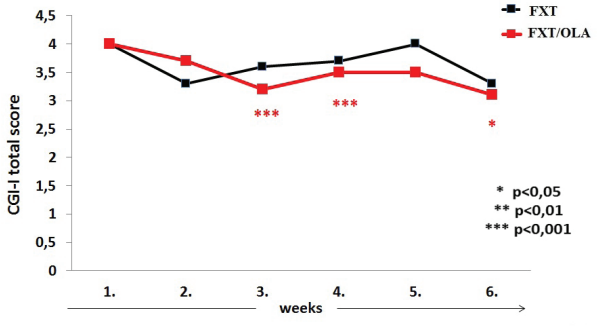


*Figure 1. b) Dynamics of clinical improvement during 6-weeks' treatment of MDD according to CGI-I scale (FXT - fluoxetine monotherapy group, FXT/OLA - fluoxetine/olanzapine combined therapy).*

greater after the 3rd week of treatment in combined therapy ($p < 0.0001$) (Figure 1.b). The most common side effects of fluoxetine monotherapy were tremor and headache, and in the combined therapy, there were side effects such as headache, increased appetite, weight gain and fatigue.

## DISCUSSION AND CONCLUSION

Our view of the literature using CDRS-R as a measure of treatment effectiveness in the paediatric population indicates

that fluoxetine monotherapy is safe and effective in the acute phase of treatment of MDD in three placebo controlled-trials (Emslie et al., 1997, 2002; March et al., 2004). On the other side, residual symptoms after the acute treatment are common, and relapse/recurrence of depression is typical for more than 30% of adolescents (DeFilippis, Wagner, 2014). According to the study of Mayes et al. (2007), there is a remission rate 41.5% in children and 32.6% in adolescents after the acute phase of fluoxetine monotherapy treatment. Fluoxetine monotherapy is probably not sufficient in treating MDD in children psychiatry. More effective therapeutic strategies are insufficient. In recent years, the combined or augmented therapeutic strategies are preferred. Olanzapine is an effective mood stabilizer and a multi-receptors antagonist with antidepressant effect that binds with high affinity to the receptors of serotonin 5HT2A/2C, 5HT6, dopamine D1-4, histamine H1 and adrenergic α1 receptors. Olanzapine is an antagonist with moderate affinity binding for serotonin 5HT3 and muscarinic M1-5 receptors. Olanzapine binds weakly to GABAA (GABAergic), benzodiazepine, and β-adrenergic receptors and can enhance antidepressant action of fluoxetine - highly specific serotonin reuptake inhibitor. This fact was demonstrated in adult studies of treatment resistant depression, which showed that the olanzapine/fluoxetine therapy is superior to fluoxetine alone (Corya et al., 2006). There are no published studies on MDD in adolescent age comparing fluoxetine monotherapy and combined therapeutic options. There is only one study in bipolar depression showing that olanzapine/fluoxetine combination was superior to placebo in the acute treatment of bipolar I depression in patients who were 10 to 17 years old (Detke et al., 2015), but no more studies are available. According to our study, both therapeutic strategies showed statistically significant effectiveness in the acute 6-weeks' treatment of MDD, but olanzapine/fluoxetine combination is more statistically significant as compared to fluoxetine monotherapy. Except this, we found that for a combined therapy, it is typical to have an earlier onset of action (after 2nd week of treatment). It is possible that the combined therapeutic strategies suggest a higher level of therapeutic effectiveness after the acute treatment, better response to the treatment, shorter time to remission and relapse prevention in patients with MDD. Similar to adult patients, clinically, the most common adverse effects of olanzapine/fluoxetine combination in our patients were increased appetite, weight gain and fatigue. Despite the known adverse effects of olanzapine medication, benefits outweigh the risks (Detke et al., 2015). Combined/augmented treatment in patients with depression is needed, and more research is necessary.

## ACKNOWLEDGEMENT

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