

Acute phase of depression treatment - current research and its perspectives on Jessenius Faculty of Medicine

Akútna fáza liečby depresie - doterajší výskum a jeho perspektívy na Jesseniovej lekárskej fakulte

Original research article

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Received 22 June, 2016, accepted 19 July, 2016

Abstract In the previous research at Jessenius Faculty of Medicine in Martin has been studied depression and its treatment from the aspects of the quality of life and functioning of the patients, as well as comparing the efficacy and safety of venlafaxine versus venlafaxine and olanzapine treatment. Last years have been studied the parameters of the autonomic nervous system in the context of depression. Our new work will build on these findings, during the exploration of efficacy and safety of a novel antidepressant vortioxetine in monotherapy and in combination with olanzapine. Since combination of vortioxetine and olanzapine is not yet understood, it is unknown whether the effect of the treatment of depressive symptoms and associated problems will be stronger and faster compared to vortioxetine monotherapy.

Slovak abstract V rámci doterajšieho výskumu na Jesseniovej lekárskej fakulte Univerzity Komenského v Martine bola skúmaná depresia a jej liečba z aspektu kvality života a fungovania pacientov, ako aj porovnanie účinnosti a bezpečnosti liečby v rámci terapeutických vetiev venlafaxín versus venlafaxín a olanzapín. Posledné roky sa intenzívne skúmajú parametre autonómneho nervového systému v rámci depresie. Naša nova štúdia má nadviazať na získané poznatky pri skúmaní účinnosti a bezpečnosti nového antidepressíva vortioxetínu v monoterapii a v kombinácii s olanzapínom. Keďže kombinácia vortioxetínu s olanzapínom nie je doposiaľ preskúmaná, nevie sa, či efekt pri liečbe depresívnych príznakov a pridružených problémov bude výraznejší a rýchlejší v porovnaní s monoterapiou vortioxetínom.

Keywords Vortioxetine – Olanzapine – Depression**Kľúčové slová:** vortioxetín – olanzapín – depresia

INTRODUCTION

In the last decade of the 20th century, the Clinic of Psychiatry of Jessenius Faculty of Medicine in Martin has been studied for depression and its treatment with SSRIs in comparison to TCAs from the aspects of the quality of life and functioning of the patients in the depression phase and remission (Ondrejka et al., 2001), later a group of psychological variables during the depression treatment (Farsky et al., 2012). Recently are studied the markers of autonomic nervous system (ANS) within depression and their relevance for psychopharmacotherapy

(Tonhajzerova et al., 2012). A clinical study of efficacy and safety of venlafaxine versus venlafaxine and olanzapine therapy of adult depression (Kulhan et al., 2014) was also realised. Based on these facts, our new study will assess efficacy and safety of vortioxetine monotherapy with combination of vortioxetine and olanzapine. This study is the result of interdisciplinary cooperation of Department of pharmacology, Department of physiology, and Clinic of Psychiatry of Jessenius Faculty of Medicine in Martin within the Biomedical center Martin.

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The project is supported by grant UK/90/2016.

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Vortioxetine is a novel multimodal antidepressant that combines the direct effect of several serotonin receptors with inhibition of serotonin transporter (SERT).

The aim of our work is to assess the dynamics of depressive and anxious symptoms during the treatment of major depressive disorder (MDD). We will also evaluate the psychological variables, such as meaningfulness, hope, loneliness, and well-being, which are not included in the diagnostic criteria for major depression, but are important for reintegration to life after depression. During the treatment, we will observe the incidence of adverse events. In addition, we will assess the selected markers of ANS, such as heart rate variability, galvanic skin response, and pupillary response, which could indicate cardiovascular autonomic dysfunction and provide information about safety of treatment. Within each therapeutic line, we will also evaluate the dynamics of executive functions using a computer psychodiagnostic tool. We will also review the incidence of comorbidity of depression and alcohol use.

METHODS

Inclusion criteria are diagnosis of depressive episode or recurrent depressive disorder according to ICD-10 classification (F32 or F33), age 18–65 years, and the ability to participate in research. The exclusion criteria are serious symptomatic disease, which could distort the results and cognitive deficit that does not allow adequate cooperation. After signing an informed consent, patients will be randomised into two equal therapeutic lines. In the first line will be patients with vortioxetine monotherapy, in the second line will be patients with combined vortioxetine and olanzapine therapy.

Depressive symptomatology will be assessed objectively by MADRS (Montgomery and Asberg Depression Rating Scale) and subjectively by BDI (Beck Depression Inventory). The anxiety symptoms will be assessed objectively by HAM-A (Hamilton Anxiety Rating Scale) and subjectively by SAS (Zung Self-Rating Anxiety Scale). We also evaluate the clinical impression by CGI (Clinical Global Impression), suicidality by C-SSRS (Columbia Suicide Severity Rating Scale), and psychological variables with the help of questionnaires as The Life Meaningfulness Scale Halama, Snyder Hope Scale, UCLA Loneliness Scale, Loneliness Questionnaire, and SEHW Scale. Patients will be assessed by scales every week, except for the psychological variables, which will be used only before and after the treatment period.

Safety and tolerability of the treatment will be evaluated every week by UKU Scale (The Udvalg for Kliniske Undersogelser Side Effect Rating Scale). Before and after treatment will be realised laboratory tests to assess selected biochemical, haematological, and coagulation parameters, and ECG focussed on QTc interval. The changes in the ANS will be evaluated by dynamics of parameters, such as heart rate variability, galvanic skin response, and pupillary response, measured before and after the treatment period. During the treatment, we will every week monitor the changes in

anthropometric parameters, such as blood pressure, heart rate, weight, and BMI.

Dynamics of the executive functions will be evaluated by the computer neuropsychological program NP3 using the tests DOTS (Dot Counting Test), HANOI (Tower of Hanoi), and SAT66 (Selective Attention Test). Alcohol use disorder will be determined as AUD by DSM-5 (Alcohol Use Disorder), HDD (Heavy Drinking Days), and by ADS (Alcohol Dependence Scale).

Gained data will be evaluated by statistical analysis. In the first step, the data distribution will be assessed by using Lilliefors test. For Gaussian distribution of data, the paired and unpaired Student test will be used. Paired Student test will be used to evaluate the pre- and post-treatment score difference of the psychological variables and executive functions. Unpaired Student test will be used to evaluate the score difference between the two treatment groups in particular weeks to examine the scales' score differences in the separate weeks. ANOVA (Analysis of Variance) of repeated measures will be used to evaluate the efficacy of pharmacotherapy in the treatment groups to test time effect on MADRS, BDI, HAM-A, and SAS score decrease. The relations will be assessed using correlation analysis. We will test the potential between-test correlations by the Pearson/Spearman correlation coefficient. The post-hoc Bonferroni correction will be used to counteract the multiple comparisons effect. The non-parametric variants of the tests will be used only in the case of non-Gaussian distributions.

The study is corresponding with ethical standards of current scientific research. All collected data will be used only for scientific purposes and personal data will not be published.

DISCUSSION

Major depressive disorder is a common disease with lifetime prevalence of 13% and incidence rate of 4% (Alonso et al., 2004). It most commonly occurs in the third decade of life, with a high relapse rate and risk of chronicity, and it is the leading cause of death by suicide. After depressive episode, often persists residual symptoms, functioning deficits, and deficits in the psychological variables, such as meaningfulness (Ondrejka et al., 2001). Despite the large number of antidepressants, the treatment of depression still has limitations, mainly in their efficacy and tolerability. Nowadays, antidepressants from the SSRI or SNRI group are the main therapeutic options in the treatment of MDD, but they often negatively affect the sexual and cognitive function, or can induce weight gain, which can lead to therapeutic discontinuation, and these interruptions increase the number of episodes and the risk of chronicity (Alvarez et al., 2014).

Arrival of vortioxetine as an antidepressant with multimodal activity in contrast with the unimodal activity of SSRI or SNRI can bring a perspective option in depression treatment. Besides SERT inhibition, it has also a direct effect on several serotonin receptors (5-HT₃, 5-HT₇, 5-HT_{1D} receptor antagonist,

5-HT_{1A} receptor agonist, and 5-HT_{1B} receptor partial agonist). In addition, experimental studies have shown that vortioxetine also increases extracellular concentration of norepinephrine, dopamine, acetylcholine, and histamine (Mørk et al., 2012). From twelve short-term randomised double-blind clinical studies that investigated efficacy of vortioxetine in MDD treatment, eight were positive (in seven studies vortioxetine was superior to placebo, in one study vortioxetine was superior to agomelatine as an active comparator), three showed no significant differences versus placebo, and one study failed (vortioxetine and active comparator were not superior to placebo) (Sanchez et al., 2015). Studies also showed good safety profile of vortioxetine with no association with clinically important changes in the laboratory test or vital signs and adverse events with incidence close to the placebo level with the highest incidence of nausea, which was typically reported during the first weeks, and it was mostly transient (Baldwin et al., 2013). From the findings of meta-analysis focussed on the incidence of the emerging sexual dysfunction reported in studies of antidepressant medications resulted that only antidepressants without serotonergic activity were able to maintain low rates of sexual dysfunction similar to placebo (Serretti & Chiesa, 2009). In the clinical studies of vortioxetine, the incidence of sexual dysfunction was similar to placebo and significantly lower than that for the active comparators, even though vortioxetine is a serotonergic agonist (Alvarez, 2014).

Vortioxetine monotherapy and combined therapy with olanzapine can be a perspective treatment option of major depressive disorder. Based on the study that showed vortioxetine was superior to agomelatine as an active comparator in patients with MDD with an inadequate response to SSRI or SNRI monotherapy (Häggström et al., 2013), we could expect that vortioxetine is an efficient alternative in treatment of patients with depression, who do not achieve a remission using the first line of treatment.

According to study of Katona et al. (2012) in elderly patients with MDD, vortioxetine showed significant improvement in cognitive neuropsychological tests of executive function, attention, speed of processing, verbal learning, and memory compared with placebo (Katona et al., 2012). It is questionable whether the combined therapy with olanzapine will affect the executive functions similarly as vortioxetine monotherapy.

Based on the results of Kulhan et al. (2014), the combination of venlafaxine and olanzapine was statistically more significant in reducing the anxiety symptoms in the third week of treatment than venlafaxine monotherapy in depressed adults. It follows that the combination of venlafaxine and olanzapine could be an alternative pharmacotherapy in management of anxiety symptoms in patients with anxious depression (Kulhan et al., 2014). Based on these findings, it is likely that olanzapine could have an augmentation effect on the antidepressant therapy. The combination of vortioxetine and olanzapine in treatment of anxious depression has not yet been investigated.

Antidepressant monotherapy in the MDD treatment is in many cases limited because of latency in the development of antidepressant effect, initial adverse events, inadequate effect on sleep disturbances, and anxiety. For this reason, it is necessary to study combinations of drugs used in psychiatry in the way of augmentation strategy or combined therapy. According to the present studies, vortioxetine is a multimodal antidepressant with good efficacy and tolerability, which can lead to better therapeutic adherence than antidepressants in the first line of treatment, where the reasons of therapeutic interruption are negative affection of sexual and cognitive functions and induction of weight gain. Despite many studies, especially randomised double-blind and placebo-controlled trials, better understanding is still needed, and complex interdisciplinary methodology of investigation can bring valuable knowledge about the depression treatment.

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