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Title: Prospective, randomized comparison of efficacy of antidepressant monotherapy and combinations of antidepressants in the treatment of patients with resistant depression.

Background: Approximately 60% of patients respond to first antidepressant treatment trial. Combination of antidepressants (CAD) is the strategy that is often used to overcome resistance to treatment in depressive patients.

The aim of the study: This randomized, 6-week, open label study compared efficacy of CAD and antidepressant monotherapies (ADM) that had been chosen according to clinical judgment of the attending psychiatrist in the treatment of patients suffering from resistant depression.

Methods: A total of 60 inpatients (intent-to-treat analysis) with major depressive disorder diagnosed according to Diagnostic and Statistical Manual of American Psychiatric Association, 4th revision (≥ 1 unsuccessful antidepressant treatment) were randomly assigned to the interventions. The responders who completed the acute phase of study, were evaluated for relapse within two months of follow-up treatment. The primary outcome measure was score change in the Montgomery-Åsberg Depression Rating Scale (MADRS), response was defined as a $\geq 50\%$ reduction of MADRS score and remission as a score of MADRS ≤ 12 points. The side effects of antidepressant treatment were evaluated using Frequency, Intensity, and Burden of Side Effects (FIBSER).

Results: Mean changes in total MADRS score from baseline to week 6 for patients in both treatment modalities were not different (ADM=13.2 \pm 8.6 points; CAD=14.5 \pm 9.5 points; $p=0.58$). There were also no differences between groups in response rate (ADM =48%; CAD=58%), remission rate (ADM= 41%; CAD=45%) and number of drop-outs (ADM- 4/30, CAD- 6/31, $p=0,30$) in acute treatment as well as proportion of responders' relapses in the follow up.

Conclusion: Both CAD and ADM treatments produced clinically relevant reduction of depressive symptomatology in acute treatment of patients with resistant depression and their effect did not significantly differ from each other. Based on our data and results of other studies, the use of CAD from treatment initiation as a first-line treatment of patients with resistant depression remains questionable.