

Combining Medications to Enhance Depression Outcomes (CO-MED): Acute and Long-Term Outcomes of Single-Blind Randomized Study

BACKGROUND

- Antidepressant medications typically result in 30 – 35% remission rates (in-placebo controlled trials) and it appears that some antidepressant medications work for some but not others.
- From a pharmacological perspective, combination therapy might act on a wider range of neurotransmitters, enhancing efficacy for some.

OBJECTIVE

- To determine whether either of two different antidepressant medication combinations would produce a higher remission rate at 12 weeks and after 7 months than monotherapy with a SSRI as first-step treatment in outpatients with chronic or recurrent major depression.

METHODS

- **Design:** Placebo-controlled, parallel, randomized, single-blind trial; Duration: 7 months
- **Inclusion Criteria:** 18 to 75 years of age meeting the clinical criteria for nonpsychotic major depressive disorder, recurrent (with current episode ≥ 2 months in duration), or chronic (current episode > 2 years) and a score of at least 16 on the 17-Item Hamilton Depression Rating Scale.
- **Exclusion Criteria:** Pregnant or breastfeeding or not using adequate birth control; history of Axis I disorders; current psychotic symptom(s); history of anorexia or bulimia; current diagnosis of obsessive compulsive disorder; current substance dependence requiring inpatient detoxification or treatment; requiring hospitalization for a psychotic disorder; history or intolerance or allergy to any protocol medicine; currently taking or a history of nonresponse to an adequate trial of an FDA-approved antidepressant; history of somatic antidepressant treatment; presence of an unstable general medical condition (GMC) that will likely require hospitalization or to be deemed terminal; requiring medications for a GMC that contraindicates any study medication
- **Primary Outcome Measures:** Remission, defined as ratings of < 8 and < 6 on the last two consecutive applications of the 16-Item Quick Inventory of Depressive Symptomatology-Self Report
- **Secondary Outcome Measures:** Side effect burden, adverse events, quality of life, social functioning, and attrition
- 665 patients randomly assigned to one of the following:
 - Escitalopram + placebo
 - Started at 10 mg/day and could be increased to 20 mg/day at 4 weeks. Placebo was started at week 2 with the option to increase it to two pills at week 4.
 - Sustained-release bupropion + escitalopram
 - 150 mg/day bupropion was used initially and increased to 200 mg/day at week 1. Escitalopram began at 10 mg/day at the week 2 visit. At week 4, the bupropion dose was raised to 400 mg/day and/or the escitalopram dose was raised to 20 mg/day. At week 6 and beyond, doses could be increased up to a maximum of 400 mg/day for bupropion and 20 mg/day for escitalopram.
 - Extended release venlafaxine + mirtazapine
 - Venlafaxine dosing started at 37.5 mg/day for 3 days and then was raised to 75 mg/day. At week 1, the dose was raised to 150 mg/day. At week 2, mirtazapine was added at a dose of 15 mg/day. At week 4, the venlafaxine dose was raised to 225 mg/day and/or the mirtazapine dose was increased to 30 mg/day. At

week 6, the mirtazapine dose could be raised to 45 mg/day. At week 8, the venlafaxine dose could be raised to 300 mg/day.

- Data handling method was intent-to-treat.

RESULTS

- Of the initial 665 patients randomly assigned to treatment, 156 were lost to follow-up (43 in the placebo group, 59 in the bupropion plus escitalopram group, and 54 in the venlafaxine plus mirtazapine group) during the acute phase. Of the 479 patients who entered the continuation phase, 58 were lost to follow-up (18 in the placebo group, 18 in the bupropion plus escitalopram group, and 22 in the venlafaxine plus mirtazapine group).
- 38.8% of patients achieved remission in the control group at week 12; remission rates were 38.9% ($p=0.99$) and 37.7% ($p=0.81$) in the bupropion plus escitalopram and venlafaxine plus mirtazapine groups, respectively.
- At 7 months, 46.0% of patients achieved remission in the control group and 46.6% ($p=0.90$) and 41.8% ($p=0.38$) achieved remission in the bupropion plus escitalopram and venlafaxine plus mirtazapine groups, respectively.
- At 7 months (or study exit, if earlier), the three groups were not different in terms of remission rate, response rate or attrition rate. Nor did the groups differ in the percentage of change in QIDS-SR, quality of life, or work and social adjustment.
- **Author's Conclusion:** There appears to be no advantage to either medication combination over escitalopram alone as a first-step treatment for non-resistant depression in outpatients with chronic and/or current major depressive disorder. Some combinations may incur a higher risk of side effects and may be dose-related.

STRENGTHS

- Large-scale study
- Objectives were consistent with the research question
- Study was of sufficient duration

LIMITATIONS

- No data provided to account for compliance
- Study group may not be representative of outpatients with chronic and/or recurrent major depression
- Doses used may not have been sufficient to realize the full potential value of combination antidepressant medications
- The results for the continuation treatment phase are limited by the fact that the subjects were not re-randomized or stratified by level of improvement following the acute phase
- Clinicians were not blind to treatment
- A structured interview was not used to establish axis I diagnosis
- Unknown why investigators chose the drug combinations they did

CONCLUSION

- Although the study showed that there appears to be no benefit of bupropion plus escitalopram or venlafaxine plus mirtazapine over monotherapy with escitalopram in patients with chronic and/or recurrent major depressive disorder, this information does not provide much insight clinically.
- Future research:

- Further studies need to be conducted using other combinations of antidepressant therapy in patients with nonresistant depression and treatment-resistant depression.

Reference: Rush, AJ, et al. "Combining medications to enhance depression outcomes (CO-MED): acute and long-term outcomes of a single-blind randomized study." *American Journal of Psychiatry* 2011; 168: 689 – 701.

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