Second-generation antidepressants, such as the selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), are considered first-line treatments for anxiety. Recent studies in major depressive disorder have suggested that antidepressants are more effective for severely depressed patients than for mildly depressed patients [1,2]. As a consequence, guidelines for the treatment of milder depression have changed. Little is known, however, about whether this relationship between baseline severity and antidepressant efficacy also holds for anxiety disorders.

**Objective:** To examine the influence of baseline severity of anxiety on antidepressant efficacy for generalized anxiety disorder (GAD), social anxiety disorder (SAD), obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and panic disorder (PD).

**Methods:** Data from Food and Drug Administration (FDA) reviews of approved second-generation antidepressants was used. All premarketing randomized controlled trials of second-generation antidepressants for the short-term treatment of an anxiety disorder were included, with the exception of three trials with incompatible primary outcomes.

Baseline symptom scores and change in symptom scores were extracted for placebo and treatment groups in each study. For PD, remission rates were also extracted. Hedge’s g was calculated from the change score and its standard deviation for GAD, SAD, OCD, and PTSD. For 10 trials, data on the standard deviation or remission rate was missing; multiple imputation was used to impute these missing data. Mixed-effects meta-regression was used to investigate the effects of treatment group, baseline severity, and their interaction on the standardized change from baseline or the remission rate (for PD only).

**Results:** Fifty-six trials with a total of 14,710 participants were included. Placebo effect sizes ranged from 0.49 for OCD to 1.03 for GAD, while drug effect sizes ranged from 0.83 for OCD to 1.35 for GAD. Increasing baseline severity did not predict greater improvement in drug groups compared to placebo groups. Standardized regression coefficients of the interaction term between baseline severity and treatment group were 0.04 (95% confidence interval −0.13 to 0.20, p = 0.65) for GAD, −0.06 (−0.20 to 0.09, p = 0.43) for SAD, 0.04 (−0.07 to 0.16, p = 0.46) for OCD, 0.16 (−0.22 to 0.53, p = 0.37) for PTSD, and 0.02 (−0.10 to 0.10, p = 0.96) for PD. For OCD, baseline severity did not predict improvement in both placebo and drug groups equally (b = 0.11, 95% confidence interval 0.05 to 0.17, p = 0.001).

**Conclusions:** No relationship between baseline severity and the drug-placebo difference was found for anxiety disorders. These results suggest that mildly or moderately anxious patients may experience as much benefit from antidepressants as severely anxious patients. The size of the drug-placebo difference was small to moderate; whether these effects may be considered clinically relevant remains a matter of debate. If considered clinically relevant, however, our results suggest that antidepressants may be prescribed to anxious patients regardless of symptom severity.

**References**


**Combining clomipramine and paroxetine for treatment-resistant obsessive compulsive disorder**

G. Amodeo1,*, G. Maina2, G. Rosso3, M. Viola1, A. Fagiolini1

1 University of Siena, Department of Molecular Medicine, Siena, Italy; 2 University of Torino, Department of Neurosciences, Torino, Italy; 3 University of Bari, Department of Neurosciences and Psychiatry, Bari, Italy

The aim of this study is to investigate safety and efficacy of the combination treatment with Clomipramine and Paroxetine in Obsessive Compulsive Disorder (OCD) resistant to monotherapy or to other associations of drugs.

OCD is the fourth most common mental disorder in the United States with an estimated lifetime prevalence of 2.5% and is identified as a major cause of long-term disability to patients and their families [1,2]. Clomipramine was the first drug approved to treat OCD and it is still used as monotherapy with a relatively high rate of success. However, clomipramine is associated with significant anticholinergic and other adverse effects, which often make them a second choice to selective serotonin reuptake inhibitors (SSRI). Paroxetine, at doses of 40 mg/die, resulted effective in treating acute OCD, while long-term administration showed to be safe to decrease the rate of relapse [3]. Unfortunately, patients do not always respond adequately to treatment with a SSRI or tricyclic antidepressant monotherapy, and augmentation strategies therefore become necessary. Combination of clomipramine and paroxetine is based on rationale that both drugs inhibit reuptake of serotonin. Moreover, the use of two concomitant antidepressants may influence other transporters and/or receptors. An increase in clomipramine plasma concentrations may be induced by paroxetine inhibition of Cytochrome P2D6 enzymes. Conversely, clomipramine, which is able to inhibit Cytochrome P2D6 enzymes as well, might increase paroxetine serum levels. However, most SSRIs are metabolized by multiple enzymes, so the inhibitor action of clomipramine may not have a substantial impact [4].

We report on the safety and efficacy of the combination clomipramine-paroxetine in twenty-four adult patients affected by resistant Obsessive Compulsive Disorder and treated with the association of clomipramine and paroxetine, at average doses of 150 mg/die and 40 mg/die respectively. Efficacy was evaluated with clinical observation and tolerability/safety was estimated through Sternbach criteria, identifying at least 3 of 10 of these features: mental status changes, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination and fever, routing out other causes (e.g., infectious, metabolic and substance abuse) and regarding that no neuroleptic had been started before the onset of the signs and symptoms listed above [5]. Cardiac activity and the length of the QTc interval were monitored in recruited subjects.

Sixteen subjects recruited (66.5%) achieved a moderate/high improvement in obsessive-compulsive symptoms without any major tolerability problem. No patients met Sternbach criteria for diagnosis of serotonin syndrome, although eleven patients presented side effects reported as mild (e.g. dizziness, tremor, dry mouth, diaphoresis). One patient had to stop treatment because of lengthening of QTc interval. Few and mild adverse effects appear to be due to clomipramine anticholinergic action, rather than the enhancing on 5-HT function induced by this combination treatment. Five patients underwent measurement of clomipramine blood levels, which resulted above the reference range (230–450 ng/ml).
We retrospectively demonstrated that the combination of paroxetine and clomipramine may be a safe and effective treatment for resistant OCD. Controlled, prospective and randomized trials are needed to confirm our preliminary findings.

References

P4.d.006 Serotonin reuptake inhibitor augmentation with N-acetylcysteine in treatment resistant OCD: a double-blind randomized controlled trial
D.L.C. Costa1*, J.B. Diniz1, M. Joaquim1, A.C. Acciarito1, B. Rodrigues1, E. Oda1, G. Requena1, E.C. Miguel, R. Gedanke Shavitt1 1Institute of Psychiatry – University of Sao Paulo Medical School, Projeto Transtornos do Espectro Obsessivo-Compulsivo PROTCOL, Sao Paulo, Brazil

Background: Obsessive-compulsive disorder (OCD) is a debilitating psychiatric condition with a lifetime prevalence of 2–3% [1]. The efficacy of serotonin reuptake inhibitors (SRIs) for obsessive-compulsive disorder (OCD) treatment has been well established in controlled studies [2]. Although most patients benefit from pharmacological treatment, up to 60% may not respond to a first trial with SRI in effectiveness studies [3]. Riluzole is an anti-glutamatergic agent that has been associated with improvement of OCD symptoms in an open-label study of SRI augmentation [4]. From this positive result, it has been hypothesized that other agents acting on the glutamatergic system could enhance the effect of the SRI in treatment-resistant OCD patients. N-Acetylcysteine (NAC), an anti-glutamatergic and anti-oxidative agent, is being considered as an add-on strategy for treatment-resistant OCD. The main objective of this study was to determine if NAC is effective in treatment-resistant OCD patients after 16 weeks of SRI augmentation.

Methods: We conducted a randomized, double-blind, and placebo-controlled trial in an OCD-specialized outpatient clinic from May 2012 and October 2014. Patients were considered eligible if they: (1) had a DSM-IV primary diagnosis of OCD; (2) failed to respond to at least one previous adequate pharmacological treatment for OCD – defined as the use of a SRI (fluoxetine, paroxetine, citalopram, escitalopram, fluvoxamine, sertraline or clomipramine) at the maximum recommended or tolerated dosage for at least 12 weeks; (3) had a baseline Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) total score ≥ 16 and their OCD symptoms were of at least moderate severity on the Clinical Global Impression (CGI) Scale. Of 145 eligible subjects, 40 (mean age= 37.9 years, SD = 10.9; male= 52.5%; mean baseline Y-BOCS score= 25.1, SD = 3.8; mean number of previous adequate treatments= 3.4, SD= 2.0) were randomized (NAC up to 3000mg per day, n=18; placebo, n=22) and 35 completed the trial. The medications that were in use at the time of randomization were maintained at the same dose. Independent assessments were conducted at baseline and at the end of the study. The primary outcome measure was the mean reduction of initial Y-BOCS scores. For this analysis, we used repeated measures ANOVA.

Trial registration: clinicaltrials.gov identifier NCT01555970

Results: Both groups showed a reduction of the baseline Y-BOCS score (mean= 3.5, SD = 7.1) at week 16, but there was no significant statistical difference between the two groups: patients who received NAC had a mean reduction of 4.3 (SD = 7.7) points, whereas those who received placebo had a mean reduction of 3.0 (SD = 6.8) points (within subjects effect: F = 1.025; p value=0.45).

Conclusions: NAC augmentation of SRI was not different from placebo in this sample of treatment-resistant OCD patients. Participant’s severity profile, indicated by the baseline Y-BOCS scores and the number of previous adequate treatments, might have influenced the results.

References

P4.d.007 Olanzapine augmentation in alleviating treatment-resistant nightmares and insomnia in patients with combat-related PTSD
G. Sulejmanpasic-Arslanagic1*, B. Bise Srebrenka1 1University of Sarajevo Clinical Center, Psychiatric clinic, Sarajevo, Bosnia and Herzegovina; 2Cantonal Psychiatric Hospital Jagomir, Psychiatric, Sarajevo, Bosnia and Herzegovina

Purpose of the study: Post-traumatic stress syndrome (PTSD) is a highly prevalent, yet poorly recognized syndrome characterized by intense reaction (fear, horror, and helplessness) to extreme traumatic stressor and it is a highly prevalent (7.8% lifetime rate) anxiety disorder [1]. Sleep disturbances are hallmark symptoms of posttraumatic stress disorder (PTSD). Subjective reports of sleep disturbance indicate that 70–91% of patients with post-traumatic stress disorder (PTSD) have difficulty falling or staying asleep. Nightmares are reported by 19–71% of patients, depending on the severity of their PTSD and their exposure to physical aggression. Studies of PTSD treatment with sertraline [2] provide evidence for its efficacy in reducing symptoms and its favorable profile of side-effects. Nightmares and insomnia in combat-related post-traumatic stress disorder (PTSD) might be resistant to treatment with selective serotonin reuptake inhibitors (SSRIs) and benzodiazepines.