inhibition) and non-significant (Linear Mixed Model; $p > 0.4$). Responders (T_0 and/or T_1) had no significant different 5-HT or NA uptake inhibition relative to non-responders (ANOVA; $p > 0.12$).

Table: Clinical and uptake-inhibition effects of paroxetine or placebo dose-escalation

	6 weeks (T_0; randomization)		12 weeks (T_1)	
	Paroxetine DE (n = 18*)	Placebo DE (n = 19*)	Paroxetine DE (n = 18*)	Placebo DE (n = 19*)
$HDRS_{17}$	20.8±7.1	19.8±5.5	15.8±6.7	14.6±8.4
5-HT-uptake	28.4±15.3	43.6±20.7	58.1±14.2	45.8±24.0
NA-uptake	16.6±13.6	19.3±14.2	39.6±15.8	25.0±20.8

Means ±SD. DE= dose-escalation.
*Due to missing values not all cells contain data for all subjects.

Conclusions: We found higher 5-HT and NA uptake inhibition after paroxetine dose-escalation, which was not statistically significant due to our modest sample size.

However, we found no clinically relevant, nor significant associations between changes in 5-HT and NA uptake inhibition and changes in $HDRS_{17}$-scores, consistent with an earlier report [2].

Limitations: We had a modest sample size and both 5-HT and NA uptake inhibition measured ex-vivo were lower than in previous reports [1;2].

We conclude that higher doses of paroxetine appear to increase ex-vivo 5-HT and especially NA uptake inhibition, but these effects do not seem to contribute largely to the improvement of MDD. These results are in line with other reports of inefficacy of higher doses of paroxetine [3].

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P.2.d. Affective disorders and antidepressants – Antidepressants (basic)

P.2.d.001 Antidepressant properties of ketamine plus imipramine treatment: behavioural and molecular studies in rats

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Introduction: Evidence is emerging for a role for dysfunctional glutamate neurotransmission via N-methyl-D-aspartate (NMDA) receptor in major depression. Researches in this area have been made out by the fact that all often used antidepressant drugs show therapeutic efficacy in a maximum of 60–70% of depressive patients, therefore there is a strong need for alternative antidepressive treatments [1]. Several studies have shown that NMDA receptor antagonists have antidepressant effect in animal models, as well as in humans [2,3]. Furthermore, other studies have showed changes in NMDA receptor subunits. Ketamine is a NMDA receptor antagonist for glutamate and has been shown to have antidepressant effects in animal models [2] as well as antidepressant effects in humans [3]. Morphological changes have been reported in hippocampus, prefrontal cortex and amygdala. One mechanism by which brain impairments may correspond with depression is via the loss of neurotrophic factors and related signaling cascades. Neurotrophic factors regulate neural growth and differentiation during development and are regulators of plasticity and survival of adult neurons and glia.

Objective: The present study investigates the possibility of synergistic interactions between antidepressant imipramine with uncompetitive NMDA receptor antagonist ketamine.

Methods: Wistar rats were treated with ketamine (5 and 10 mg/kg) and imipramine (10 and 20 mg/kg) and then subjected to the forced swimming test by Porsolt's test and open-field test to assess possible effects of drug treatment on spontaneous locomotor activity. The Cyclic AMP response element binding protein (CREB) and brain-derived-neurotrophic factor (BDNF) protein levels and Protein Kinase C (PKC) and Protein Kinase A (PKA) phosphorylation were assessed in prefrontal cortex, hippocampus and amygdala by imunoblot. CREB, BDNF, PKA and PKC are involved in major depression and antidepressants treatments.

Results: Imipramine at the dose of 10 mg/kg and ketamine at the dose of 5 mg/kg did not have effect in the immobility time ($p > 0.05$ by ANOVA); however, the effect of imipramine (10 and 20 mg/kg) was enhanced by both doses of ketamine ($p < 0.05$ by ANOVA) and did not modify the number of crossing and rearing compared to saline treated-rats. Combined treatment with ketamine and imipramine produced stronger increase of CREB and BDNF protein levels in prefrontal cortex, hippocampus and amygdala ($p < 0.05$ by ANOVA) and PKA phosphorylation in hippocampus and amygdala and PKC phosphorylation in prefrontal cortex ($p < 0.05$ by ANOVA).

Conclusion: In conclusion, this present study indicates that co-administration of antidepressant imipramine and NMDA receptor antagonist ketamine may induce a more pronounced antidepressive activity than treatment with imipramine alone. Our study may be very important in the case of drug-resistant patients, and to produce a rapid onset antidepressant action. In addition, we suggested that synergistic effect by ketamine plus imipramine in BDNF and CREB protein levels and PKA and PKC phosphorylation may be involved in regulation of NMDA receptor.

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