According to WHO, over 300 million people worldwide are affected by depressive illness. The most prevalent and disabling form of depression is major depressive disorder (MDD). Despite several decades of research on antidepressants the number of patients suffering from MDD is constantly growing. In the USA, between 2005 and 2010, prevalence of MDD rose from 13.8 million to 15.4 million adults and the direct costs incurred by individuals with MDD increased by 27% during that time (from 77.5 billion USD in 2005 to 98.9 billion USD in 2010). Treatment of depression is expensive but social costs are also huge. Patients with MDD have limited ability to take up education and employment. They are often excluded from the society. At its worst, MDD can lead to suicide. According to WHO, about 800 000 people die due to suicide every year.

Although currently used antidepressants (selective serotonin reuptake inhibitors and selective serotonin norepinephrine reuptake inhibitors) are much safer for patient than the drugs used a few decades ago, their effectiveness, especially for the MDD, is not higher. These drugs require several weeks of systematic administration to obtain a therapeutic effect. Another problem is a large percentage of drug-resistant patients (30%). In addition, in the case of some patients who do not respond to any of the available treatments, including electroconvulsive therapy, medicine is helpless. Therefore, the discovery a new, effective, rapid-acting antidepressant is one of the key tasks of modern psychopharmacology.

In the face of these data, the discovery of the rapid antidepressant action of ketamine should be considered as a breakthrough. Ketamine causes not only a rapid (within hours) and long lasting antidepressant effect, but also shows efficacy in the treatment-resistant patients who have often been treated for a long time without success. Interestingly, S-ketamine received the breakthrough therapy designation from the U.S. FDA for MDD with imminent risk for suicide.

Unfortunately, ketamine also induces undesirable effects. It is a psychoactive agent classified as a dissociative drug and similarly to other substances in this group (e.g. phencyclidine, nitrous oxide) can cause feelings of detachment from the environment and self. Hence, its recreational use as a psychostimulant can be a problem. Therefore, research is being undertaken to limit or eliminate these effects. Recent studies indicate that several potential strategies can be used to achieve this goal, including the use of ketamine enantiomers or ligands of glutamate-dependent receptors (so-called mGlu receptors), which may potentiate the therapeutic effect of ketamine. In this project, we have combined both strategies. The main purpose of our research is to determine the potential role of selected ligands of mGlu receptors in intensifying or accelerating the antidepressant action of ketamine and its enantiomers. To accomplish this task, we decided to use a well-developed and recognized animal model of depression based on the mild stress. In addition, a series of behavioral tests will be performed to investigate potential adverse effects.

These studies can significantly contribute to lowering the therapeutic dose of ketamine and minimizing the side effects associated with its use. As a further consequence, this can contribute to the development of a new antidepressant drug, that is highly effective, its action is quick and sustained and at the same time does not cause significant adverse effects.