

## **Research and Development of the Novel Antipsychotic Aripiprazole**

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A pathogenesis of schizophrenia has not been established; however, hyperactivity of dopaminergic neurotransmission is presumed to play a major role (dopamine hyperactive theory). Thus, in past years, a number of drugs with dopamine receptor antagonistic activity were developed, including chlorpromazine and haloperidol. These drugs were so-called typical antipsychotics. Research in psychopharmacology has continued to concentrate on the development of improved antipsychotics capable of providing significant improvement in terms of clinical efficacy and side-effect profile over typical antipsychotics. The development of clozapine introduced the concept of atypical antipsychotics, and it was subsequently followed by development of serotonin-dopamine antagonists, the first of which was risperidone and also included olanzapine, quetiapine and ziprasidone. Although the development of these atypical antipsychotics resolved some of the efficacy and safety issues of typical antipsychotics, they were still unable to fully satisfy the clinical requirements for schizophrenia treatment.

In 1972 Professor Arvid Carlsson proposed the existence of presynaptic dopamine autoreceptors that negatively regulate dopamine synthesis, release and firing of dopaminergic neurons. Based on the dopamine hyperactive theory of schizophrenia, Otsuka Pharmaceutical firstly initiated research on dopamine autoreceptor agonists in the late 1970s. This research evolved into developing novel compounds that exhibit agonistic activity at presynaptic dopamine autoreceptors and antagonistic activity at postsynaptic dopamine D<sub>2</sub> receptors. The result of this research was aripiprazole, a novel antipsychotic with dopamine D<sub>2</sub> receptor partial agonistic activity. Aripiprazole is the first antipsychotic which has been proven to be clinically effective without being a D<sub>2</sub> receptor antagonist. Today's presentation will review the history of the research and development of aripiprazole and present the pharmacological and excellent clinical data of aripiprazole.