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Limitations of existing antipsychotic therapies

R Tandon*

Address: Professor of Psychiatry, director, Schizophrenia Division, Department of Psychiatry, University of Michigan, US
* Corresponding author

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The clinical profiles of atypical and conventional antipsychotics can be understood in terms of their different pharmacological profiles. All of the currently available effective therapies for treatment of schizophrenia affect dopaminergic transmission. The conventional antipsychotics are antagonists of D_2 receptors. Although effective for reduction of positive symptoms of schizophrenia, these agents have minimal effect on negative symptoms and may exacerbate them. In addition, nonselective dopamine blockade with these agents causes a variety of adverse effects, particularly extrapyramidal symptoms (EPS), tardive dyskinesia, prolactin elevation and related side-effects. The newer, atypical agents also have D_2 antagonistic properties, but are associated with significantly lower risk of EPS and tardive dyskinesia, and are more effective for reduction of negative symptoms than conventional antipsychotics. The exact pharmacologic basis for atypicality is a subject of debate, but involves activities at other receptors, particularly 5-HT2A, different binding kinetics to D_2 receptors, or the combination of the two. The atypical agents are, however, only partially effective in treating negative and cognitive symptoms; furthermore, they are associated with weight gain and metabolic changes, sedation, effects on cardiac conduction, etc. that may ultimately have serious medical consequences as a result of increased risk for cardiovascular events and diabetes.