

Novel Antischizophrenia Treatments

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1. Auflage 2012. Buch. X, 455 S. Hardcover
ISBN 978 3 642 25757 5
Format (B x L): 15,5 x 23,5 cm
Gewicht: 859 g

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Preface

Six decades after the serendipitous discovery of chlorpromazine as an antipsychotic and four decades after the launch of clozapine, the first atypical or second-generation antipsychotic, psychopharmacology has arrived at an important cross-road. Revealing the different modes of action of available antipsychotics on biochemical, electrophysiologic, neuroanatomic, and behavioral grounds has not only helped to develop new medications with improved tolerability but also contributed to our understanding of mechanisms relevant for psychosis in general and schizophrenia and bipolar disorder in particular. It is remarkable in this context the extent to which such research has moved towards using imaging techniques and more empirical clinical assessments. Although research targeted at specific receptors and pathways of antipsychotic drug action has extended our knowledge considerably, it remains true that all currently approved antipsychotic drugs share one common mechanism, i.e., dopamine D₂ receptor antagonism. There is still uncertainty as to whether first- and second-generation antipsychotics can really be separated and if the assumed progress exemplified by newer compounds is sufficient to survive the challenges of evidence-based medicine. Although the use of antipsychotics has become safer, adverse metabolic and cardiac effects remain as major issues in the clinic and in the development of new agents. It became clear that all clinically used antipsychotic medications are effective in treating positive symptoms, but certainly not for negative symptoms and also not for the core cognitive deficits that have been widely neglected in research in the time between Kraepelin and the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative.

The efforts to develop antipsychotics based on D₂ receptor antagonism in combination with effects on other receptors (with or without intention) have remained the focus of the last two decades. It is clear that pharmacological research and pharmaceutical development must now focus on complementary or even alternative mechanisms of action to address unmet medical needs, i.e., poorly treated domains of schizophrenia, improved acceptance by patients, better adherence to medication, safety in psychoses in demented patients, and avoiding cardiac and metabolic adverse effects. The first completely novel mechanisms evolving

from our insights into the pathophysiology of psychotic disorders, especially the role of glutamatergic mechanisms in schizophrenia, are now under development, and further principles are on the horizon. This situation, in many respects similar to that when the initial second-generation antipsychotics became available, can be rewarding for all. Preclinical and clinical researchers now have the opportunity to confirm their hypotheses and the pharmaceutical industry may be able to develop really novel classes of therapeutics.

When we were approached by the publishers of the *Handbook of Experimental Pharmacology* to prepare a new volume on antipsychotics, our intention was to capture both the accumulated preclinical and clinical knowledge about current antipsychotics as well as prospects for new and potentially more specific antischizophrenia principles. These efforts should be based on the pathophysiology of the diseases and the affected neurotransmitter systems. Since preclinical research on antipsychotic compounds is only reliable when intimately linked through translational aspects to clinical results, we decided to include clinical science as well. It turned out that that this endeavor could not be covered by a single volume. We thank the editorial board and the publishers for supporting our decision to prepare two volumes: *Current Antipsychotics* and *Novel Antischizophrenia Treatments*. These topics cannot really be separated from one another and should be seen as a composite entity despite the somewhat arbitrary separation of contributions into two volumes. The continuing challenges of developing improved and safer antipsychotic medications remain of concern and are discussed in the first volume. The new opportunities for the field to develop and license adjunctive treatments for the negative symptoms and cognitive deficits that are treated inadequately by existing compounds have been incentivized recently and provide the focus for the second volume. We hope these collective contributions will facilitate the development of improved treatments for the full range of symptomatology seen in the group of schizophrenias and other major psychotic disorders.

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