

effective treatments for deliberate self-harm patients. Larger trials are badly needed.

## SES14. AEP Section "Psychopharmacology": From receptor pharmacology to clinical prescription

Chair: M. Ackenhil (D)

### SES14.01

FROM RECEPTOR PHARMACOLOGY TO CLINICAL PRESCRIPTION: ANTIDEPRESSANTS

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In the advent of modern antidepressant drug therapy we have moved from early empirical serendipity of tentative compounds in the middle of the past century to understanding of details in the pharmacodynamic actions of several CNS-monoamine enhancing such drugs as of today. The result of this progress is that a number of very effective clinical antidepressants are now available, but still there is need for improvements in this important psychiatric treatment armamentarium. However, should this be achieved primarily by introduction of yet other novel potential antidepressant compounds or is there now room for development of another conceptual approach towards drug development in counteracting major depressive disorders? The latter statement is supported by important factors to consider in the naturalistic clinical setting like problems with patient compliance with prescription of antidepressant agents and multiple possibilities for drug-drug interactions to occur due to common polypharmacy in this scenario, factors that would not change only if newer compounds are to be the future solution for optimising antidepressant drug therapy. By preference, a new conceptual scientific effort should be guided by a strive towards defining better strategies for individual dose optimisation procedures in the future.

Accordingly, in parallel with pursuing traditional pharmacological receptor research it is today necessary to focus also on delineating neglected clinical psychopharmacological issues of the established antidepressant drugs. To these issues belong a better definition of e.g. the many pharmacokinetic changes that may occur in clinical reality, as well as to improve our understanding of why these changes are brought about and when they may even be hazardous to a certain group of patients or the single individual prescribed such drug therapy. The rapidly escalating knowledge of details in drug metabolic features for antidepressant drugs and clinical application of techniques such as Therapeutic Drug Monitoring (TDM) and cytochrome P-450 (CYP) genotyping procedures based on these scientific fundaments therefore bears a great promise for the future development of advancing clinical antidepressant pharmacology into a more closely prescription-related research.

In recent years, therefore, the situation in this scientific field has come to change focusing more and more on antidepressant dosology in a clinical context. To this end, introducing "clinical outcome" studies recording concentration- rather than dose-related drug effects in both in vivo in animal models as well as in phase III-IV human trials have become essential tools in this process. Underlying motives and state-of-the-art for this antidepressant drug development that is complementary to traditional receptor pharmacology giving rise to an approach of "psychopharmacological holism" will be conveyed in the present lecture. This include a brief

survey of the utility for TDM and CYP-genotyping methodology in clinical practice when treating affective disorders.

### SES14.02

FROM RECEPTOR PHARMACOLOGY TO CLINICAL PRESCRIPTION: ANTIPSYCHOTICS

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The receptor binding properties of the new antipsychotics (risperidone, olanzapine, sertindole, quetiapine and ziprasidone) plays a critical role to explain the clinical profile of these drugs. All of them share 5HTA2/D2 antagonism, but they bind also to other multiple different receptors. D2 antagonism is related to both clinical efficacy on positive symptoms and extrapyramidal side effects and the antagonism of 5HTA2 receptors may be responsible of clinical efficacy on negative signs and symptoms of schizophrenia and reduced extrapyramidal side effects. The different binding profile on other receptors can be related to specific clinical and unwanted effects and can lead to a better clinical prescription if we consider the overall consequences but not the effect of the antagonism of one specific receptor. The binding affinities of the new drugs are:

Olanzapine: high for D4, 5-HT2A, 5-HT2C (high-moderate), 5-HT6, M1, M4 and alpha 1; moderate for D3; low for D2, 5-HT7 and H1.

Risperidone: high for D2, D3, D4, 5-HT2A, 5-HT7 and alpha 1; low for 5-HT2C, 5-HT6, M4 and H1.

Quetiapine: high for H1, 5-HT2C, 5-HT6 and 5-HT7; moderate for 5-HT2A and alpha 1; low for D2, D3, D4 and M4.

Sertindole: high for D3, D4, 5-HT2A, 5-HT2C, 5-HT6, 5-HT7 and alpha

1; moderate for D2; low for M4 and H1.

Ziprasidone: High for D2, D3, 5-HT2A, 5-HT6, 5-HT7 and alpha 1; moderate for D4, 5-HT2C and H1; low for M4.

The overall effect v.s. single binding consequences can be represented by the sedating effect of quetiapine. There is general agreement that H1 antagonism induces a high degree of sedation but quetiapine increase the release of tele-methyl-histamine via 5-HT2 antagonism and the clinical consequence is a low sedating effect.

### SES14.03

PRACTICAL PROBLEMS WITH CO-PRESCRIPTION: PROBLEMS WITH EFFICACY

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Polypharmacy, the simultaneous prescription of several drugs is the usual treatment for most of the psychiatric patients. In the mean each patient is treated with 3 psychotropic drugs, additionally with medicaments for somatic diseases like e.g. hypertension (betablockers, AT<sub>1</sub>-inhibitors, α-Blockers). Many of these drugs show interactions, both on the level of pharmacokinetic and pharmacodynamic. Such combinations through different mechanisms can diminish the therapeutic efficacy. Augmentation strategies utilize such interactions to shorten the response delay or to overcome non response. However, most of the co-medication lack any scientific evidence and even are contradictory.

The availability of new specific drugs leads to frequent combination. For depression, new SSRIs are prescribed together with classical antidepressants, lithium and mood stabilizers. Non response due to too high plasma levels or to pharmacodynamic interactions are resulting. Schizophrenic and manic patients are treated with