The development of antidepressants that appear to selectively affect either serotonin or norepinephrine has renewed interest in distinguishing neurotransmitter systems and coupling them with clinical phenomenology. Parallel to this development, a number of investigators have documented differences in response to antidepressants among depressive subtypes. For the delusional subtype there is some consensus on the specifics of treatment response. Delusional depression may not respond sufficiently to treatment with antidepressants alone but often requires combination with antipsychotics or electroconvulsive therapy (ECT). It has also become more and more clear that selective serotonin reuptake inhibitors (SSRIs) and some other types of never antidepressants are relatively ineffective for treating depressed inpatients. When treating inpatients, the superiority of tricyclic antidepressants (TCAs) compared to never antidepressants is evident, especially in studies using sufficient doses of TCA. Perhaps most intriguing are the data that suggest that depressed patients of the melancholic (endogenous) subtype does not respond adequately to SSRIs but does respond to TCAs and to ECT. This paper will discuss these aspects emphasizing the Danish University Antidepressant Group studies comparing TCAs and SSRIs.

S31.02

The fate of moclobemide

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The introduction of the reversible monoamine oxidase-A inhibitor moclobemid was a promising development of the MAO inhibitor principle in the treatment af major depression. The irreversible MAO inhibitors has severe interactions with a broad range of drugs and patients needs to be very alert regarding specific dietary components such as redwine, cheese and so on. In spite of investigations showing promising results and a very beneficial side effect profile, the drug is currently not much used. This presentation reviews the principal studies included the DUAG study on moclobemide and tries to explain the fate of moclobemid.

S31.03

Dose-effect relationships for antidepressants

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Dose-effect studies provide, for groups of patients, information on the probability of therapeutic response and tolerability problems (non tolerability) for different doses and varying duration of therapy.

By such studies it thus may be possible to describe the inter-patient variability in intended and unintended effects and therapeutic range or index of the compound examined.

In several reviews and studies on different types of antidepressants it has been concluded that a dose with optimal balance between intended and unintended effects cannot be indicated, since the dose-effect curves for antidepressant effect and adverse reactions are flat and overlapping. (Gram, NEJM, 1994, 331: 1354, Bollini & al. BJP,1999, 174: 297, DUAG-4, CPT 1999, 66: 152).

For TCA such as clomipramine dose-dependant kinetics and genetic polymorphisms are important. However, for clomipramine the concentration-effect relationship was not better than the dose-effect relationship, suggesting that the variation in dose-effect is as much related to other factors than kinetic variability.

Data on clomipramine (DUAG-4, 1999) suggested that higher doses, not only are more effective, but also is associated with faster response. Indeed higher doses are also associated with more frequent tolerability problems causing drop-out. Clinical dosing should be based on a judgment of the patient's need for rapid effective cure, against the importance of good tolerability.

S31.04

Placebo-controlled relapse prevention trials in unipolar depression

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Among the treatment modalities in the acute therapy phase of a major depressive episode, ECT (electroconvulsive therapy) has the highest response rate (90%), but also the highest relapse rate in the continuation phase over the next 6 months (65%). Placebo has the lowest response rate (45%), but the highest pharmacological relapse rate (50%). The SSRIs seem to have the lowest relapse rate compared to imipramine (12% versus 30%). Both the SNRIs and mirtazapine (the ''dual action'' drugs) have higher relapse rates (20%) although they have a higher response rate than the SSRIs (70% versus 60%).

S31.05

Prophylaxis in bipolar disorder: methodological implications of an almost completed lamotrigine-vs-lithium study

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Background and Aims: In 2 drug approval studies lamotrigine has been shown to possess prophylactic potentials comparable with lithium in bipolar disorder. However, the generalisabilty of these results are limited. In 2001, an investigator-driven study was initiated comparing lamotrigine and lithium for prophylaxis aiming at mimicking routine clinical conditions. Data collection is not completed (until end 2006) albeit recruitment is accomplished. Based on preliminary findings, the focus will be on methodological implications.

Methods: This is an open, multicenter, randomised trial conducted within the Danish University Antidepressant Group Subjects suffered from bipolar disorder indicating prophylaxis. Exclusion criteria were kept to a minimum. Randomisation took place when clinically appropriate The primary end-point was the need for additional medication or hospitalization, conditionally that patients were stabilized on monotherapy 6 months after randomisation. Patients were followed up to 6 years after randomisation.

Results: Of the 155 randomised patients, 123 (79%) were recruited at the main center. So far, 25% of the patients were prematurely withdrawn within the first 6 months after randomisation, 25% were withdrawn at 6 months since they were not in monotherapy at this point, 25% have reached the primary end-point and the remaining 25% are still in trial.

Conclusions: The large proportion of patients that needed additional medications even after 6 months indicates that previous long-term studies randomising patients on monotherapies may have limited generalisability. The uneven contribution from the main center and the other centers indicates that multicenter studies may include patients that are selected beyond the selection criteria.

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