Orals

86. Antidepressant – Clinical I

86-1 Prevalence and management of rapid metabolizers of antidepressants (AD's)

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The prevalence of AD rapid metabolizers was estimated by reviewing charts of depressed patients treated with tricyclic antidepressants (TCA's). Ultra-rapid metabolizers were managed by inhibiting metabolism in order to achieve plasma levels.

Methods: *Study 1:* The charts of 198 TCA-treated (mostly with desipramine) patients with available plasma levels were reviewed. Given the standard dose range of 150–300 mg for most TCA's, and the accepted therapeutic plasma level range of 550–1100 nmol/L (150–300 ng/ml), rapid metabolism was defined: compliant patients with plasma TCA < 500 nmol/L at doses up to 300 mg/d, and who remained depressed. *Study 2:* In 17 ultra-rapid metabolizers of desipramine, one of the cytochrome P450 2D6 inhibitors fluoxetine (n = 8), paroxetine (n = 6), or quinidine (n = 3) was added to desipramine to raise desipramine levels to the therapeutic range.

Results: 1) Twenty-one (21%) of referred patients treated with a TCA were rapid metabolizers. 2) The combination strategy to inhibit P450 2D6 activity achieved desipramine levels nmol/L in 15/17 ultra-rapid metabolizers. Twelve of these 15 patients (80%) achieved "excellent" or "good" relief of depression.

Conclusions: Ultra-rapid AD metabolism may commonly contribute to "treatment resistance." Inhibiting enzymatic metabolism of TCA's, resulting in higher plasma levels, achieve therapeutic response in most patients.

86-3 A double-blind trial of nefazodone versus placebo in depressed inpatients

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Objective: To investigate the utility of nefazodone to treat severely depressed inpatients.

Method: Flexible doses of nefazodone (100–600 mg/day) and placebo (1–6 tablets/day) were compared for 6 weeks in 81 inpatients (41 nefazodone, 40 placebo) who met DSM-III-R criteria for nonpsychotic Major Depression and who required psychiatric hospitalization.

Results: Severity of illness was reflected in baseline values for the Clinical Global Impression (CGI) Severity score (5.0 nefazodone, 4.9 placebo), the 17-item Hamilton Depression Rating Scale (HAM-D-17: 29.7 nefazodone, 29.8 placebo), the Montgomery Asberg Depression Rating Scale (MADRS: 39.0 nefazodone, 38.6 placebo) and the presence of melancholia (98% nefazodone, 93% placebo). At endpoint, nefazodone was superior ($p \leq 0.01$) to placebo on the HAM-D-17 (mean change: −13.5 nefazodone, −6.1 placebo), the number of patients exhibiting at least a 50% decrease in HAM-D-17 score (54% nefazodone, 18% placebo), the CGI Improvement (% 'much' or 'very much improved': 56% nefazodone, 25% placebo) and Severity scores (mean change: −1.6 nefazodone, −0.9 placebo), and the MADRS (mean change: −17.8 nefazodone, −7.7 placebo). Significant differences were noted by week 1 on several rating scales. Mean modal doses at endpoint were 500 mg with nefazodone and 5.4 tablets with placebo. Five placebo-treated patients (13%) and four nefazodone-treated patients (10%) discontinued for adverse experiences. Nineteen (48%) in the placebo group and 12 (29%) in the nefazodone group discontinued for lack of effect.

Conclusion: Nefazodone is effective in the treatment of severely depressed hospitalized patients.

86-4 A randomized, double-blind comparison of mirtazapine and fluoxetine in patients with major depression

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Aim: To compare the efficacy and tolerability of mirtazapine and fluoxetine in depressed in- and outpatients.

Methods: Patients with a Major Depressive Episode (DSM-IIIR), a baseline score of ≥21 on the 17 item-HAMD and ≥22 on depressed mood item, were randomized to a 6 week treatment with either mirtazapine (n = 66) or fluoxetine (n = 67). Efficacy was evaluated by the HAMD, CGI and the Visual Analogue Mood Rating Scale (VAMRS), and the effects on sleep by the Leeds Sleep Evaluation Questionnaire. The efficacy analyses were performed on the Intent-To-Treat Group using the Last Observation Carried Forward method.

Results: Mean total 17 item HAM-D scores at baseline were 26.0 for mirtazapine and 26.1 for fluoxetine-treated group. The decrease from baseline on the the HAMD was larger in the mirtazapine than in the fluoxetine group throughout the treatment period (endpoind change −14.2 and −10.3, respectively), reaching statistical significance at weeks 3 and 4. Similar numbers of patients dropped out due to adverse events (Aes); tolerability profiles were similar.

Conclusion: The Results demonstrate that mirtazapine is more effective than fluoxetine in depressed patients with high HAM-D baseline scores, whereas the tolerability profiles are similar.

86-5 Pirlindole, a selective RIMA: An overview of its pharmacological and clinical antidepressant profile

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Pirlindole is a tetracyclic compound that acts as a selective and reversible inhibitor of monoamine oxidase A. Its MAO-B/MAO-A IC50 or ED50 ratios are respectively equal to 208 and 7.8 (for moclobemide these values are respectively 170 and 9.8). It has been shown to be active in several preclinical tests predictive of antidepressant properties (Porsolt's model, self-stimulation of the median forebrain bundle, reserpine-induced blepharoptosis, apomorphine-induced hypothermia, 5-hydroxytryptophan-induced head twitches, ...). From the clinical point of view its efficacy and safety have been demonstrated in a double-blind randomized placebo-controlled trial. In double-blind reference-controlled trials equivalent efficacies have been measured for pirlindole and most of the tricyclic antidepressants. However, pirlindole appeared safer as it did not induce anticholinergic side effects. Pirlindole has been shown to be significantly more effective than mianserin. More recently a therapeutic equivalence has been demonstrated between pirlindole and moclobemide with some tolerance advantages (e.g. less anticholinergic side effects) in favour of pirlindole. Pirlindole is actually in late clinical phase III in major depression.

86-6 High placebo response rate versus clinical impression with the new antidepressant duloxetine

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Duloxetine is a potent inhibitor of serotonin and norepinephrine uptake[1] and was speculated to have superior therapeutic efficacy in the treatment of depression. In previous open-label clinical studies response rates after 6 weeks of active therapy were approximately 80%, with good safety and tolerability results.[2,3] An 8-week double-blind study was developed to compare the efficacy of fixed doses of duloxetine (5, 10 and 20 mg/day) with placebo and clomipramine (150 mg/day); to assess the dose-response relationship of duloxetine and to compare the safety of the compounds. In South Africa 124 patients who met the DSM-III-R criteria for unipolar major depression were recruited. The results showed that there was a high placebo response rate and that duloxetine did not differentiate from placebo. Adverse events were of mild or moderate severity and were often transient in nature. The efficacy results differ from the high response rates in the open-label