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# S21. Reversible inhibitors of MAO-A. New clinical findings
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## RIMAS IN THE TREATMENT OF SOCIAL PHOBIA

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Social phobia is characterized by an extreme fear of being scrutinized by others, and often leads to avoidance of social situations. The Epidemiologic Catchment Area (ECA) study estimates the six-month prevalence for social phobia at 0.9% to 1.7% for men and 1.5% to 2.6% for women. Patients with social phobia are at increased risk for depression, substance abuse, and impairment of their social, vocational, and academic functioning.

Several studies have indicated the efficacy of monoamine oxidase inhibitors (MAOIs) in treating social phobia. Unfortunately, MAOIs are associated with a number of intolerable side effects. Additionally, MAOIs can be toxic in overdose.

The new reversible inhibitors of monoamine oxidase-A (RIMAs) may offer clinicians greater treatment options for their patients with social phobia. Moclobemide and brofaromine have a much more favourable side effect profile. There is no need for the extensive diet and medication restrictions patients must follow when taking MAOIs, and the RIMAs have not indicated any toxicity in overdose. RIMAs have proven efficacy in the treatment of depression and panic disorder. Recent research suggests RIMAs have a place in the treatment of social phobia as well.

RIMAs offer a more tolerable side effect profile, in addition to no risk of food and drug interactions or toxicity in overdose as seen with MAOIs. This has important ramifications in terms of patient compliance to treatment. If the favourable preliminary results of RIMA efficacy on social phobia are supported through further research, clinicians will be able to offer patients new treatment options.

## TREATMENT OF RESISTANT DEPRESSION

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In the treatment of resistant depression it is firstly important to clarify whether predisposing factors are present such as physical disease, use of drugs (including alcohol) or more fundamental mental illnesses such as schizophrenia.
If a recognized antidepressant has been unsuccessful when given for an adequate length of time (eg eight weeks) at full therapeutic doses, then an alternative antidepressant may be deployed. Where compliance is suspect (eg on tricyclic antidepressants) then one should consider exhibiting an antidepressant with minimal side effects such as a reversible inhibitor of MAO A. A further option is to combine two recognized antidepressants.
At some stage the introduction of lithium should be considered, adding it either to one recognized antidepressant or to two. Adjunctive treatments include T3, L-tryptophan and mood stabilizers other than lithium. If the above measures prove unsuccessful then further options are electro-convulsive therapy and neuroleptic drugs (even in the absence of any schizophrenic features).
So far we have rehearsed the alternatives in the domain of physical treatments. It is important that psychological measures should be enlisted simultaneously, and the possibilities include psychotherapy, cognitive therapy, environmental improvements and community support. In order to prevent the emergence of therapy resistant depression, doctors should be educated more in the thorough treatment of depression in the first place (Paykel & Priest), 1992).

Reference

Paykel ES, Priest RG. Recognition and management of depression in general practice: consensus statement. Brit Med J 1992; 305: 1198-1202.

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**ANTIDEPRESSANT EFFICACY AND QUALITY OF LIFE IN DEPRESSION**

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The efficacy of moclobemide (300-450 mg/day) was compared with fluoxetine (20-40 mg/day) in a double-blind, multicentre study in 209 patients with new episodes of depression, selected from consecutive depressed patients (N=612) representative of those consulting psychiatric services. Antidepressant efficacy was assessed with the Hamilton Depression Rating Scale (HDRS), Montgomery-Åsberg Depression Rating Scale and Clinical Global Impression (CGI). Medical Outcome Study Short-Form General Health Survey (SF-20) and 15-D Measure of Quality of Life were used to measure effectiveness in terms of health-related quality of life. Efficacy was evident with both drugs, with 67% in the moclobemide group and 57% in the fluoxetine group having a reduction in HDRS of more than 50%. Similarly, 77% of the patients in the moclobemide group and 67% in the fluoxetine group were assessed on the CGI as 'much better' or 'very much better' after six weeks treatment. The most commonly reported adverse events were nausea, other gastrointestinal symptoms, nervousness, dizziness and sleep disorders. Nausea was significantly more common in the fluoxetine group, and was found especially in women. Premature terminations of treatment were 18% in the moclobemide and 21% in the fluoxetine group. A significant change for the better in quality of life was found in both treatment groups, even at week two but especially after six weeks of treatment. Improvement was not only seen in dimensions measuring depression or mental health, but in other dimensions.

**SAFETY OF MOCLOBEMIDE: A CLINICAL UPDATE**

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The safety of moclobemide, a reversible, short-acting inhibitor of MAO-A, has been documented in a large number of clinical studies. However, recently cases of serotonin (5-HT) syndromes caused by interaction with clomipramine or serotonin selective reuptake inhibitors (SSRIs) have been reported.
A review is given on interaction studies (healthy volunteers, post marketing surveillance data, spontaneous clinical reports) regarding safety and risks when combining moclobemide with SSRIs or serotonin-selective tricyclics (TCAs) like clomipramine.
Summarizing, it can be concluded and recommended as follows:
A switch (sequential treatment) from SSRIs and TCAs other than clomipramine to moclobemide without a wash-out interval seems to be safe and without major risks of 5-HT-syndrome-like adverse events if the dose of moclobemide is below 300 mg/d.
Co-administration (concurrent, concomitant, simultaneous treatment) of these drugs should be avoided since clinical data are not yet sufficient devoiding 5-HT-syndrome-like adverse events.
Simultaneous use of moclobemide and clomipramine should be strongly avoided, caution is warranted in the case of sequential (switch) treatment.

*COMPARATIVE EFFICACY OF SSRI AND MOCLOBEMIDE (RIMA) IN MAJOR DEPRESSIVE DISORDER - META-ANALYSIS OF STUDIES*

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The advent of selective 5-HT-reuptake inhibitors (SSRI) has to be considered as an advancement in the therapy of depression by comparison to classical tricyclic antidepressant (TCA) treatment. A further bench-mark in this field of research represents no doubt the development of reversible MAO-A inhibitors (RIMA) of which moclobemide is to be considered as prototype. The efficacy of moclobemide by comparison to TCA has been demonstrated in a large number of double-blind comparative and placebo-controlled studies. Here we report a meta-analysis of double-blind controlled studies of moclobemide (RIMA) and SSRI (fluoxetine, fluroxamine) in major depressive disorder(DSM-III and III-R). The analysis has been performed in order to evaluate: a) the overall efficacy of these two classes of drugs, b) efficacy in subgroups of patients defined by either agitation-retardation factor scores (HAMD-17, Angst et al. 1993) or severity of depression at baseline. Additional variables tested were previous therapy with TCA, duration of illness, as well as duration of the present episode, co-medication with BDZ and possible family load.
The results indicating comparative efficacy of SSRI and moclobemide will be presented and discussed.

**Randomized, double-blind, parallel, multicentre study of moclobemide vs. clomipramine in depressive patients in general practice.**

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A double-blind, randomized, fixed dose study with ratings every second week during the 6 week´s active treatment period. Depressed patients requiring treatment and fulfilling the criteria of defined scores on the Hamilton Depression Rating Scale - 17-items - (HDRS) (see below) were examined with regard to inclusion/exclusion criteria. Eligible patients were started on a one week wash-out period, drug free. At the end of the wash-out period a diagnostic and quantitative depression rating was performed. Patients still fulfilling the inclusion criteria (HDRS total scores: 11 points or more) were stratified according to HDRS total scores HDRS between 11 and 15 and HDRS 16 points or more. Within each group, patients were allocated to double-blind therapy with a fixed dose of either moclobemide 400 mg/day or clomipramine 150 mg/day, in two equal doses per day in 6 weeks. Comparison of the therapeutic response categories defined on basis of total rating scores (complete: HDRS <7, partial HDRS: 8-15 or no response: HDRS <16. Diagnostically the patients were classified according to DSM-III-R (major depression). In addition UKU side effect scale and global rating scales (CGAS-Clinical GlobalAssessment of Severity of Illness, CGAT-Clinical Global Assessment of Efficacy) were used.
Results and conclusions:
In total 147 patients were included in the study. Only data concerning the 94 patients who had a HDRS total score above 15 are presented. Forty-eight of these patients received clomipramine, 46 moclobemide. The study revealed no significant difference in the therapeutic effect of moclobemide in comparison with clomipramine. Treatment with clomipramine results in a higher frequency of side-effects, a higher drop-out rate due to unwanted effects and was generally less tolerated than moclobemide.

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