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The Efficacy of Moclobemide (1977–1994)

A Meta-Analysis

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1. Introduction

In 1976, when medical research on the drug moclobemide (Ro 11–1163) was launched, the world-wide sales of antidepressants was dominated by tricyclic antidepressants. Monoamino oxidase inhibitors (MAOI) had a constant market share of just two percent. MAO inhibitors were considered to be less effective in the treatment of depression than standard antidepressants and were recommended for so-called “atypical” depression, which was an ill-defined syndrome. MAO-inhibitors were considered to be mere second or third choice drugs, in cases of resistance to one or two standard tricyclics. This did not change over decades until, with the development of reversible inhibitors of MAO-A (RIMA), a new area of research was started. The first few clinical trials showed that the diet necessary for treatment with MAOI’s was not necessary for patients being treated with the RIMA moclobemide, allowing an immense advantage.

In 1977, I was the first investigator to treat patients with moclobemide in an open study. I used a daily dosage of 450 mg, which is still a recommendable starting dosage today. Over the last 17 years, I have had the opportunity to treat many patients in hospital as well as ambulatory patients in my praxis and I have been administering moclobemide to special patients for a considerable number of years now. The original potential good efficacy and extremely good tolerability associated with moclobemide has been fully confirmed during its development over this period.

The aim of this paper is to review the controlled clinical research conducted on the efficacy of moclobemide over the past 27 years. This review will concentrate on a meta-analysis, report methodological problems and present the relationship between severity and efficacy. Further, the efficacy in diagnostic subgroups of depression will be analysed, including specific syndromes and single symptoms and the predictors of response. Finally the conclusions will be stated.

2. Purpose

Our purpose over the past few years has been to analyse data provided by Roche, Basle in our research unit at the Psychiatric University Hospital, Zurich, Switzerland. The aim was to obtain, independent of the drug company, a new view of the efficacy of moclobemide and put forward new questions in a meta-analysis regarding drug response. A number of studies were aggregated. We were mainly interested in the relationship between severity at baseline and drug efficacy. We monitored the placebo response vs the drug response and tried to explain the differences in the outcome of placebo controlled studies. Further, we analysed in detail the effect of moclobemide in diagnostic subgroups and focused attention on various symptoms: for example, agitation vs retardation, psychotic vs non-psychotic and suicidal symptoms.

The data provided by Roche, Basle consisted of 42 studies, of which 39 were single blind trials, 2 double-blind and 1 an open study. The data bank today now comprises of 3,367 patients. A large group of patients were analysed: 340 patients under placebo, 1,795 patients under moclobemide and 619 under imipramine. Recently, we have received data from a large double-blind study that was carried out by Guelfi et al. (1992) in France. This study compared hospitalised depressive patients treated with moclobemide (N=61) to patients treated with clomipramine (N=66). On the whole, we analysed about 3,500 patients.

The comparative studies follow different designs. There are three group studies comparing moclobemide, imipramine and placebo and two group studies comparing moclobemide vs placebo, and moclobemide vs imipramine and other antidepressants.

3. Methodology

In the analysis of efficacy, this paper focuses on two measures of response. Response was defined after 4 weeks of treatment by an improvement of at least 50% of the baseline score, measured by the Hamilton 17 Item Rating Scale for Depression (HAMD). A second measure of response was the Clinical Global Assessment of Efficacy. A positive response was assumed if, at the end of the 4 weeks period, the global judgement indicated a good or very good overall improvement.

On the whole, there is a good correlation between these two measures of response, which is independent of the baseline severity of depression. For this correlation all cases on the databank were used and the correlations varied between 0.6 and 0.73. They did not show a systematic relationship to the severity of baseline, prior to treatment.

4. Severity of Depression

Severity of depression at baseline is an important variable that needs to be taken into account in such an analysis. Therefore, we subdivided the sample into four equally sized subgroups of severity: very low¹, low², medium³ and high⁴. As a consequence, severe depression with a baseline Hamilton score of 28 or more, was found to be present in 35.6% of the population.

To account for possible drop-outs during the 4 weeks of treatment, the last measure from the Hamilton Rating Scale was taken for analysis. Our study, therefore, applied an intent to treat analysis and avoided the loss of any patients seen at least twice after the initial baseline assessment.

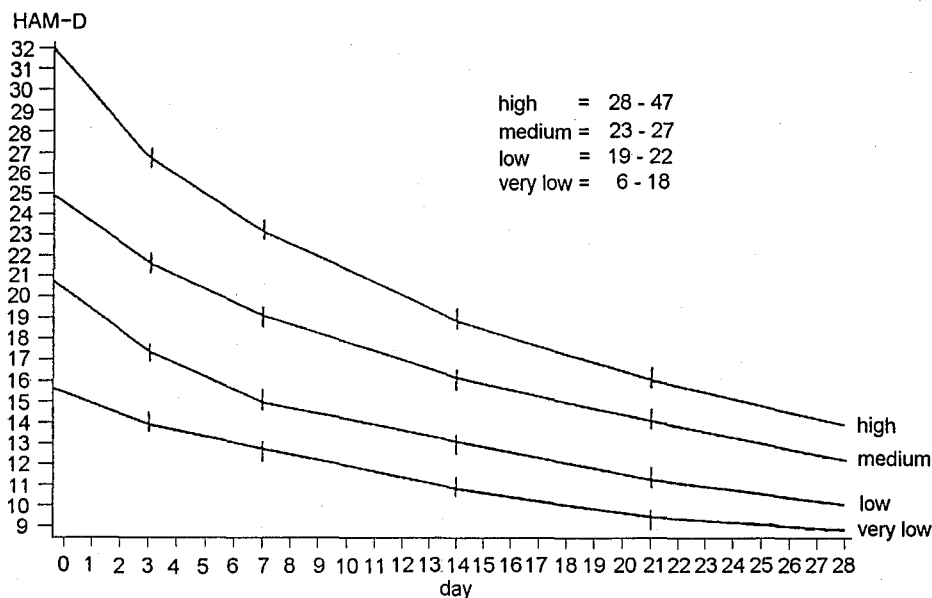


Fig. 1. Mean values of total scores of HAM-D for the four subgroups of severity of depression over the 28 day treatment with moclobemide

Reference:

Angst J.; Stassen HH.: Methodische Aspekte von Studien zur antidepressiven Wirksamkeit. In: Steinberg R., Philipp M., Möller HJ. (Ed.). Spezielle Aspekte der antidepressiven Therapie. Neuere Ergebnisse zu Moclobemid. MMV Medizin Verlag GmbH, München 1994

Severe vs less severe or mild depressives improved under moclobemide in a systematic manner throughout the 4 weeks. The most marked decrease was observed during the first two weeks of treatment (fig. 1). There is no visible difference in the shape of the curves, dependent on the baseline severity; at least there is no indication that a more severe group would respond less well

baseline score: ¹ 6-18, ² 19-22, ³ 23-27 ⁴ ≥28

than the mild depressive group. Under placebo, the shape of the curves are markedly different. There was an initial improvement during the first week, but thereafter, the mean values of the curves do not show a substantial decrease. The slight improvement during the first week can be viewed as an expression of the spontaneous process, whereas under moclobemide a clear drug induced improvement continued over all four weeks in an impressive way.

From reviews of other drug trials, we know that differently controlled trials can yield very different results. It is not unusual when an efficacious drug does not indicate any significant differences to placebo in one or more trials. Nevertheless, in the majority of controlled trials, a difference is usually visible. It is an important task to try to explain such differences.

Table 1 compares the Hamilton 50% response rates of 7 double-blind studies of moclobemide vs placebo, the results of which have already been published. Moclobemide was clearly superior to placebo in four studies, whereas in three other studies, the differences were relatively small. What are the reasons for such discrepant results? One reason could be provided by the diagnostic classification, which correlates with severity. In the first study by Casacchia, severe endogenous depressed patients were treated and here the difference between placebo and moclobemide was very pronounced. In two rather more negative studies, one by Ose in Norway and Larsen in Denmark, reactive depressives were treated and, therefore, less severe states of depression were focused on.

Table 1. Response (% of patients) to placebo, and moclobemide, and TCA, number of drop-outs

References	Depression	Drop-outs		HAM-D 50%		Comparison TCA
		placebo	Moc.	placebo	Moc.	
		%		%		
Casacchia	ED	56	> 28	0	< 56	57 ¹⁾
Versiani	MDD	12	> 9	30	< 61	
Ose	ND, RD	36	> 46	24	< 29	60 ²⁾
Botte	DYS, ED	46	> 9	13	< 35	
Larsen	RD	28	> 27	22	< 32	60 ³⁾
Bakish	MDDR	42	> 18	36	< 56	60 ³⁾
Silverstone	MDDR	35	> 33	41	< 48	45 ¹⁾

¹⁾ Imipramine, ²⁾ Clomipramine, ³⁾ Amitriptyline

ED = endogenous depression Dys = dysthymia

ND = neurotic depression MDD = major depressive disorders DSM-III

RD = reactive depression MDDR = major depressive disorders DSM-III-R

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Angst J.; Stassen HH.: Methodische Aspekte von Studien zur antidepressiven Wirksamkeit. In: Steinberg R., Philipp M., Möller HJ. (Ed.). Spezielle Aspekte der antidepressiven Therapie. Neuere Ergebnisse zu Moclobemid. MMV Medizin Verlag GmbH, München 1994

Table 2 breaks down the four studies available on our data-bank by severity at baseline. As already mentioned, Casacchia's study consisted mainly

of severe depressed patients, while Versiani's Latin America study took an intermediate position and the studies by Ose and Botte dealt mainly with mild depressed patients. There is a relationship visible between the power of the studies and severity. In studies of severe depression, the discrimination between placebo and moclobemide was highest; it was best in the first study by Casacchia, intermediate in the studies by Versani, which dealt with major depressives and studies by Botte, which dealt with endogenously depressed patients and lowest in Ose's study, which dealt with neurotic and reactive mild depressives. The conclusion of this analysis verifies that severity at baseline may be one of the most critical variables explaining differences in the outcome of trials between placebo and active compounds.

Table 2. Intent-to-treat analysis by severity

	N	Severity			HAM-D 50%		Diff
		low	medium	high	Placebo	Moc.	
					N = 234	N = 238	
%	%	%	%	%			
Casacchia	34	11	18	71	0	56	high
Versiani	486	30	35	35	30	61	interm
Ose	68	69	31	0	24	29	none
Botte	47	55	21	23	13	35	interm

Another factor is drop-out rates, which differ from study to study. In trials displaying the superiority of moclobemide over placebo, the drop-out rate under placebo was decidedly higher, as illustrated by the results of the study by Casacchia, Botte from Belgium and Bakish from Canada. It is also interesting to view the wide variation in drop-out rates between all of the studies, as presented in table 1.

Following this line of investigation, we pooled all the placebo cases and classified them into seven subgroups by severity at baseline. Fig. 2 gives the response rates. The findings are very interesting and confirm the systematic decrease of response to placebo with increasing severity at baseline. Mild depressives with a baseline score of 15 or less responded in 41% of cases to placebo, and mild depressives with a baseline score of up to 18 responded in the famous 33% of all cases. This figure corresponds to the overall estimate of placebo response by depressive patients in general. But, the slide illustrates clearly that the more heavily depressed patients respond less well to placebo; between 25 and 16% of cases.

This decrease is even more pronounced if patients who received benzodiazepines in addition to placebo are excluded (Table 3). Mild depressive patients with a baseline score of less than 23, responded in 37% of cases to placebo, whereas moderate and severely depressed patients under placebo

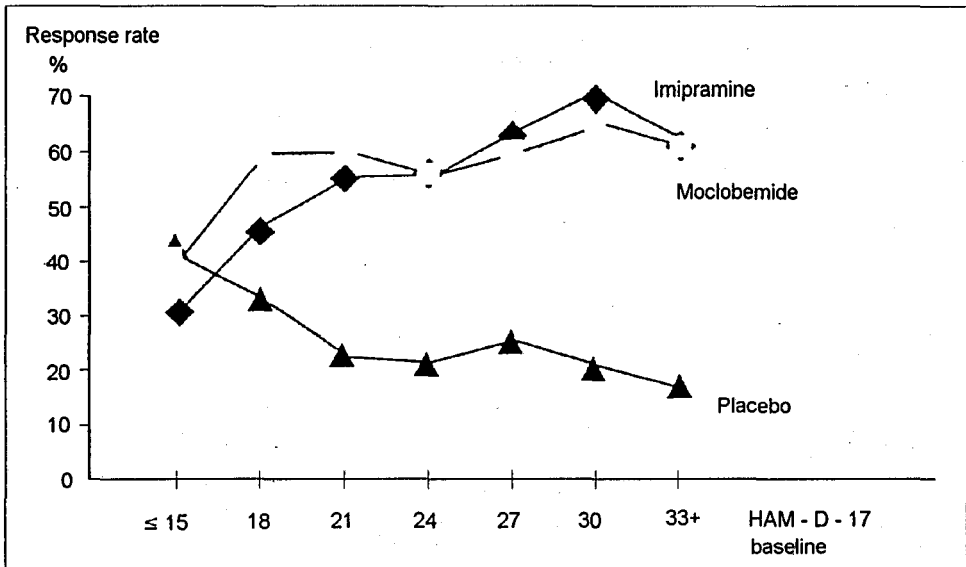


Fig. 2. Severity at baseline and response rate over 4 week treatment with placebo, moclobemide and imipramine

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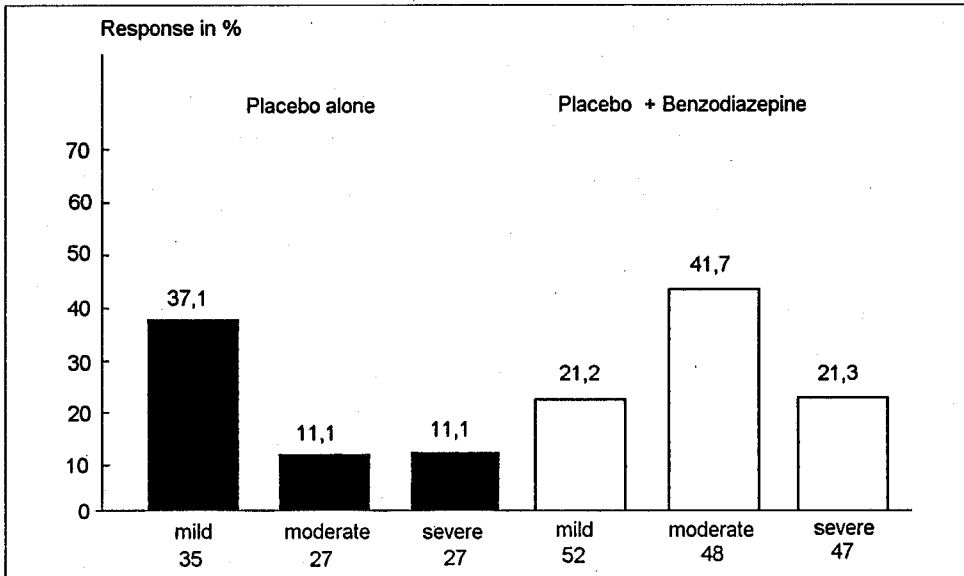
Angst J.; Slassen HH.: Methodische Aspekte von Studien zur antidepressiven Wirksamkeit. In: Steinberg R., Philipp M., Möller HJ. (Ed.). *Spezielle Aspekte der antidepressiven Therapie. Neuere Ergebnisse zu Moclobemid.* MMV Medizin Verlag GmbH, München 1994

alone responded in only 11% of cases. In contrast, patients receiving a combination of placebo plus benzodiazepines showed a response in 20–40% of cases, independent of severity. Benzodiazepines improved not only sleep, but also anxiety and agitation, as measured by the Hamilton Rating Scale.

Now what about the dependence of the response to moclobemide or imipramine on baseline severity of depression. Figure 2 also shows the data for moclobemide. Mild depressives respond in 39% of cases, a rate which doesn't differ from 41% for placebo. But patients with a higher baseline score, up to 33 or more, show about the same high response rates, in two thirds of cases. It is remarkable that there is no decrease in efficacy with increasing severity of depression.

Figure 2 shows the same findings for imipramine patients. Again, the response rate is low in the mild depressed group and does not differ from placebo, but then there is a steady increase in efficacy up to 60–70% in severe depression. The curves of the two active compounds, moclobemide and imipramine do not differ.

In summary, the data show that with increasing severity of depression, a decrease of response to placebo and the increase of response to active antidepressants is most impressive and it is clear that imipramine and moclobemide do not differ in efficacy at all.

Table 3. Placebo and benzodiazepine: Response in %. Comparison between mild, moderate and severe depression**Reference:**

Angst J.; Stassen HH.: Methodische Aspekte von Studien zur antidepressiven Wirksamkeit. In: Steinberg R., Philipp M., Möller HJ. (Ed.). *Spezielle Aspekte der antidepressiven Therapie. Neuere Ergebnisse zu Moclobemid*. MMV Medizin Verlag GmbH, München 1994

Furthermore, we can learn from these results that drug trials focusing on mild depressive patients have no chance of differentiating between active antidepressants and placebos, under the conventional measures of efficacy. This is a very critical statement, because double-blind studies with placebo are frequently carried out in mild depressive patients and may, therefore, yield negative results, as illustrated before by the drug trial on reactive depression conducted by Ose in Norway. An exception in this respect, was the large Latin America study published by Versani and co-workers, which dealt with 486 patients suitable for intent to treat analysis. This study contained an equal proportion of mild, moderate and severely depressed patients and obtained a clear difference in response rates; 30% for placebo and 61% for moclobemide. Developing countries usually recruit more non-pretreated, so-called drug naive, new patients and, therefore, have a better chance of producing a conclusive result. Such patients are usually less selected and more representative than, for instance, subjects who are recruited through advertising in industrialised countries.

5. Onset of Action

Having proven the efficacy of moclobemide against placebo, especially in moderate and severe depression, the question of onset of action arises. There is a myth surrounding psychiatry today, a hypothesis mainly raised

by American investigators, suggesting it takes "weeks" until an antidepressant takes effect, in contrast to placebo (Quitkin et al., 1987). Some researchers have even developed biochemical hypotheses in an effort to explain the supposed delayed onset of action.

From a clinical point of view, the onset of action of a drug has great practical value. It is an important factor in deciding how long a patient should be kept on the same medication, if he shows no signs of improvement. Another important question is whether antidepressants differ in their onset of action. Are there any drugs that exhibit a more rapid action? This should be one of the target aims for the development of new drugs, after all an earlier onset of action has been claimed for a number of drugs.

As clinicians, we can observe an improvement in depression in the majority of successful treatments, within the first two weeks, but research hasn't paid much attention to this phenomenon. To investigate the onset of action, one has to conduct multiple observations over the first two weeks and, above all, to define the onset of action. The onset can be defined as the first clinically meaningful improvement detected by the patient or environment. This first improvement should be maintained and should not represent a mere expression of the random fluctuation of the pathological state. Unfortunately, there is no research data available on the uncertainty (due either to observer or instrument) inherent in the clinical assessment of psychopathology. To research this area, one would need at least three baseline assessments over several days. As this information is lacking, we estimated the fluctuation from day zero to day 3 and found a variation of between 10 and 15%. This provided us with an estimate of a 20% baseline reduction as a measure of first improvement. This estimate is provisional and may be changed, i.e. if more data is collected systematically prior to treatment.

In contrast to the onset of improvement, which we defined as a 20% reduction from baseline on the Hamilton Rating Scale for depression, response was defined as a 50% reduction. As clinicians we were interested in investigating not only the time it takes for improvement to take effect, but also in the predictability of this in assessing final drug response. We were also interested in the development of final responders, for example, how many subjects improved within the first ten or fourteen days.

Early descriptions of the antidepressant efficacy of imipramine by Kuhn (1978) stressed that many patients on this drug respond within the first few days or first two weeks of treatment. This fact has been stressed again and again over the last few decades, and the myth about the delayed onset of action has been cast aside.

In our hospital, it is usual to discontinue unsuccessful treatment with patients not showing any change within the first two weeks of treatment. Such

Onset of improvement: Imipramine versus Moclobemide and Placebo

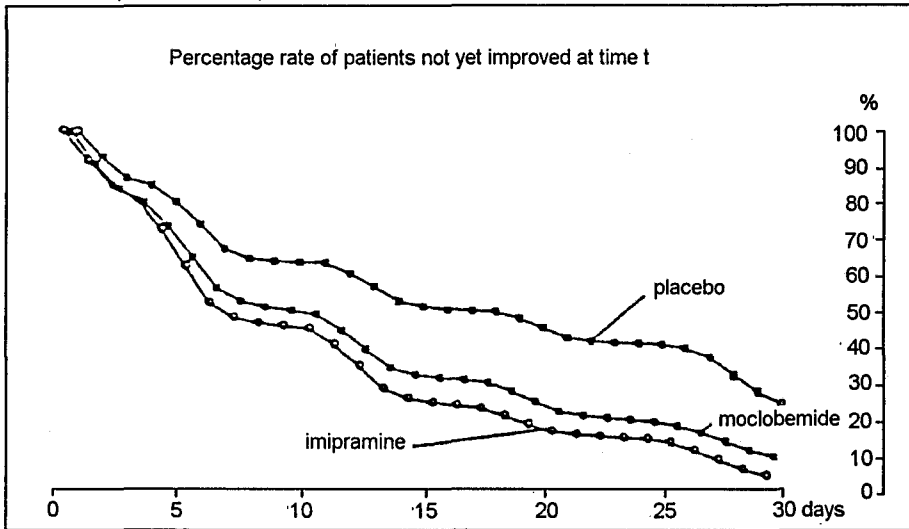


Fig. 3. Survival analytically-derived time courses of improvement under imipramine, moclobemide and placebo as reflected by the percentage rates of patients not yet improved on any given observation day

subjects are usually drug-resistant. It is similarly difficult and ethically questionable whether treatment should be maintained with outpatients, if it proves unsuccessful over a number of weeks.

Figure 3 shows the time course of improvement defined as a 20% reduction from baseline under placebo, moclobemide or imipramine. The curves represent the results of the survival analysis, and describe the cumulative percentage of patients not yet showing any improvement. Differences between active treatment and placebo emerged within the first 5 days and reached a degree of maximum distinction around day 14. After this point in time, the differences between treatment modalities remained constant until the end of the observation period.

Quantitatively, an improvement within the first two weeks was predictive of a final good response after four weeks, in 80% of patients under active treatment and 60% of placebo responders (Table 4). From the point of view of final responders, 70% improved within the first ten days. This data clearly disproves the hypothesis put forward by Quitkin et al. (1987), but confirms the results of other investigators, for example Khan et al. (1989) and Katz et al. (1987). In our analysis of the different drugs, moclobemide, imipramine and amitriptyline, we could not find any differences in the speed of onset of action. Just 30% of final responders did not show an improvement within the first ten days and, therefore, the likelihood of improving in weeks 3 & 4 was considerably lower.

Table 4. Predictive value of early onset for later outcome during 4 weeks of treatment

	Imipramine (N = 506)	Moclobemide (N = 580)	Placebo (N = 191)
Improvers	428 (84,6%)	467 (80,5%)	116 (60,7%)
Responders	314 (62,1%)	344 (59,3%)	61 (31,9%)
Patients showing improvement within first 14 days	348 (81,3%)	374 (80,1%)	90 (77,6%)
later became responders	277 (79,6%)	292 (78,1%)	55 (61,1%)
Responders who showed improvement within first 14 days	88,2%	84,9%	90,2%

6. Indication for Moclobemide

Having proven the efficacy of moclobemide against placebo, in particular in moderate and severe depression, the question of the generalisability of the action arises. This issue is highly applicable in this context, because MAO inhibitors used to be applied in a limited area only.

In most of the protocols of studies, drug companies seek to exclude bipolar patients from trials, because they are afraid of inducing drug-induced hypomania. According to our studies, the risk of doing so is extremely low; most of the switches are not drug induced at all, but due to the spontaneous course of the disorder. There is, therefore, no rational basis for excluding bipolars from drug trials. In the databank provided by Roche, a number of bipolars were included and treated with moclobemide, as well as a small number of subjects treated with imipramine and placebo.

A meta-analysis shown in figure 4 gives a response rate of 20% for bipolar and 23% for unipolar depressive patients treated by placebo. The drug treated groups (moclobemide and imipramine) revealed a three-fold higher response rate and was about the same for bipolars and unipolar depressives. Unipolar depressed patients consisted of subjects meeting the DSM-III criteria for major depressive disorder. In the light of the very low switch rate observed, moclobemide can certainly be recommended as a treatment for bipolar depression.

The association of major depressive disorder with dysthymia is called double depression. This comorbid form of depression elicits a response different to pure dysthymia. Pure dysthymia is a more chronic disease and manifests a lower drug response than double depression or other more severe and acute forms of depression. This trend is illustrated by figure 5. Both drugs were tested: moclobemide and imipramine. The group sizes were certainly large enough to be conclusive. The placebo response recorded for double depression (a severe form of depression) was slightly lower than for dysthymia. The response rates after 4 weeks of treatment are not the final response rates. Treating dysthymia correctly requires months and in the second month of

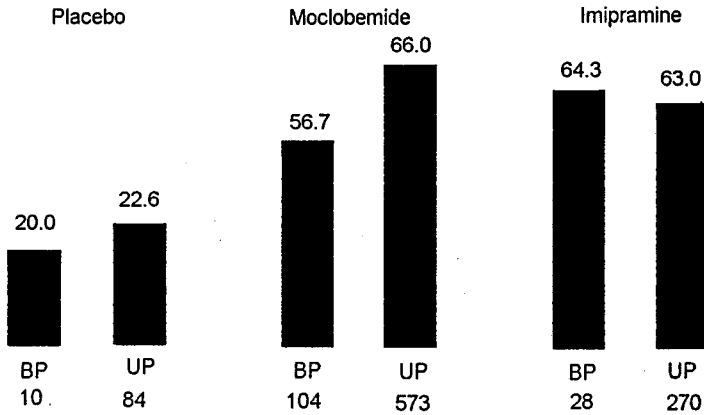


Fig. 4. Bipolar - Unipolar: Response%

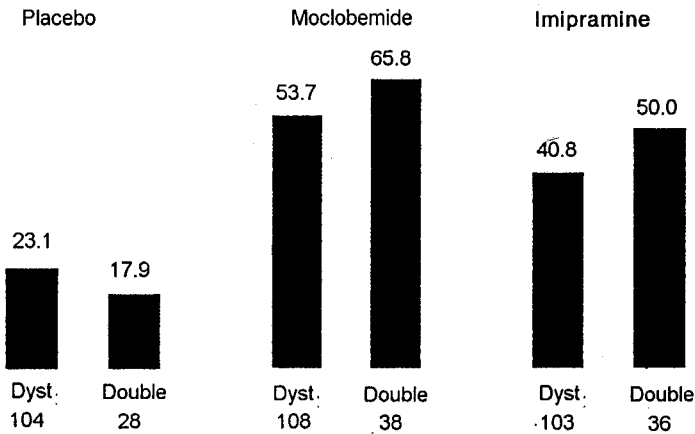


Fig. 5. Dysthymia - Double Depression: Response %

treatment there is usually a considerable gain of improvement and drug response. Treatment should, therefore, be maintained for as long as possible. Community studies have shown that pure dysthymia is rare, but the risk of developing double depression is high. The distinction between neurotic and reactive depression is diagnostically soft. As mentioned, all patients had to meet the criteria for major depressive disorder. Systematic differences emerged in the response rates to moclobemide and imipramine. The rates were slightly lower for reactive depression under placebo and moclobemide, but higher under imipramine. As mentioned, some of these placebo controlled trials dealt with very mild depressives, and were clearly not suitable subjects for proving the efficacy of an antidepressant. Yet, it is nevertheless recommendable to prescribe neurotic and reactive depressive patients with antidepressants.

In summary, our meta-analysis has shown that moclobemide and imipramine, in contrast to placebo, provide successful treatment for a wide spectrum of depressive disorders: bipolar, unipolar, dysthymia and double depression, neurotic and reactive depression and major depressive disorders. Data has also been made available on the efficacy of so-called "atypical" depression, which has also shown good efficacy under these antidepressants. Infact, we do not yet know of any subgroup of depression that does not respond favourably to moclobemide. Patients, as a rule, should be treated for as long as they manifest symptoms, even if only to a minor extent, for instance mild insomnia or mild lack of energy. Due to the relapse risk after an episode, it is sensible to continue treatment for another couple of months. Treatment length, in general, should last at least six months, and in view of the good tolerability of moclobemide compared to tricyclic antidepressants, this time length is quite feasible. For this reason, compliance is usually very good and capabilities are not impaired, such as driving a car.

In practice, the main problem in treatment is being sure to prescribe high enough doses. We recommend a starting dose of 300 mg in the morning and 150 mg in the evening, totalling 450 mg as an initial dose for ambulatory patients. This dose should be adhered to for a week and then increased to 600 mg (not more than 900 mg) if the response is poor. The patient should show mild improvement during the first ten days, if not, the dose should be sharply increased. If the response is poor, one is inclined to prescribe benzodiazepines in addition to moclobemide, instead of merely increasing the dosage of moclobemide, but this procedure is not at all recommendable; it doesn't improve the treatment results, as will be shown later.

7. The efficacy of single symptoms

Moclobemide is a non-sedative antidepressant and as such embodies great advantages as already mentioned in the context of driving ability. There is a myth circulating in psychiatry that non-sedative antidepressants should preferably be administered to retarded and sedative antidepressants to agitated patients. We have carried out extensive analyses devoted to this myth, and have found it to be simply not true.

Agitation can be defined by the agitation item on the Hamilton Rating Scale with a certain cut-off. For example, a score of two or more indicates agitation, characterised by motor restlessness. The results are shown in figure 6. Agitated depressives responded badly to placebo with a response rate of just 5%, which was the lowest rate we observed. Retarded depressives, in contrast, responded in 20% of cases. Surprisingly, moclobemide was equally efficacious in both agitated and retarded depressives. We had expected to find a better response in retarded patients. In a next step, we carried out a factor analysis of all Hamilton rating scale data available in the databank prior to treatment.

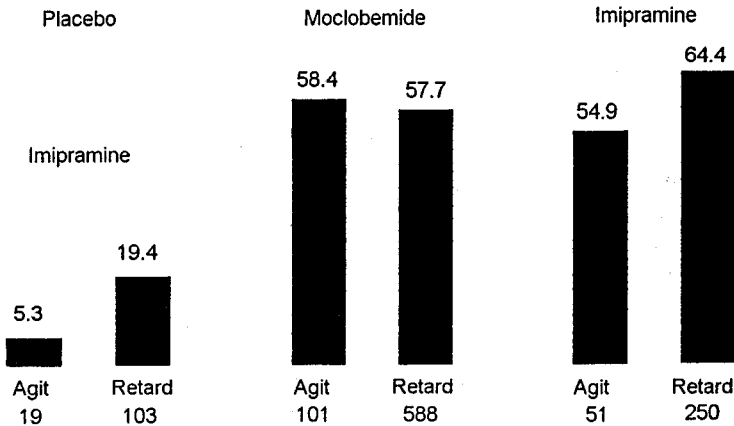


Fig. 6. Agitated - Retarded: Response %

This came up with a two factor solution; the retarded depression and the agitated retarded depression factor. The second factor includes agitation and all symptoms of anxiety: psychic-somatic, somatic, gastro-intestinal and general as well as hypochondriasis. These two factors are both stable across random samples of the depressed population.

If we subclassify patients on the **Hamilton factor "agitation/anxiety"** into three classes: low, medium, high, we obtain the same response rates to different types of drugs in all three groups. We examined moclobemide, imipramine and so-called sedative antidepressants, for instance: amitriptyline, maprotiline and mianserine. Again, we found no difference in the response rates between patients with low and high agitation scores and there was also no difference between subclasses of antidepressants. We also controlled for the effect of benzodiazepines. Agitated depressives received more benzodiazepines, but this was true for all antidepressants, even for the sedative group. Infact, sedative antidepressants were less well tolerated than non-sedative antidepressants. The conclusion is simple: moclobemide is suitable for agitated as well as for retarded depressive patients.

Another area of interest is the reaction elicited by moclobemide with **suicidal subjects**: can moclobemide reduce the suicidal symptoms or increase the risk of suicide attempts? The suicidal symptoms assessed by the Hamilton Rating Scale include suicide ideation and suicide attempts. Patients without ideation, those with ideation and those with a previous history of suicide attempts responded equally to placebos and there was no difference in the generally higher responder rates for moclobemide. Subjects with a previous history of suicide attempts, responded slightly better to moclobemide than non-suicidal subjects. For this reason, there is no rationale for excluding suicidal patients from treatment. If a patient is actively suicidal, he has to be treated in hospital.

In an analysis of placebo controlled trials, we were interested in the frequency of suicide attempts during treatment. The data indicated no difference between placebo, moclobemide and imipramine over the first 4 weeks of treatment. If we consider the whole databank, we obtain a suicide attempt rate of 0.17% over the first 4 weeks under moclobemide, compared to placebo 0.29%. Over six hundred patients were treated by imipramine, with a suicide attempt rate of 0.48. The number of suicide attempters is so small that all the differences are non-significant. Thus, we can conclude that moclobemide does not increase the risk of suicide attempts during acute treatment.

Obsessive compulsive disorder is a condition difficult to treat and with this in mind, we analysed obsessive-compulsive symptoms separately. It is interesting that the severity of this symptomatology influences the response elicited to placebo extensively (fig. 7). Patients with more severe obsessive compulsive symptoms displayed a much lower response to placebo than patients who did not manifest obsessive compulsive symptoms. A similar trend was observed with imipramine, with a systematic decrease from left to right, i.e. from zero to severe obsessive compulsive symptomatology. In contrast, moclobemide did not yield any decrease in efficacy in over ninety subjects manifesting obsessive compulsive symptoms, compared to other groups. There have not been any specific trials available on obsessive compulsive disorder up to now.

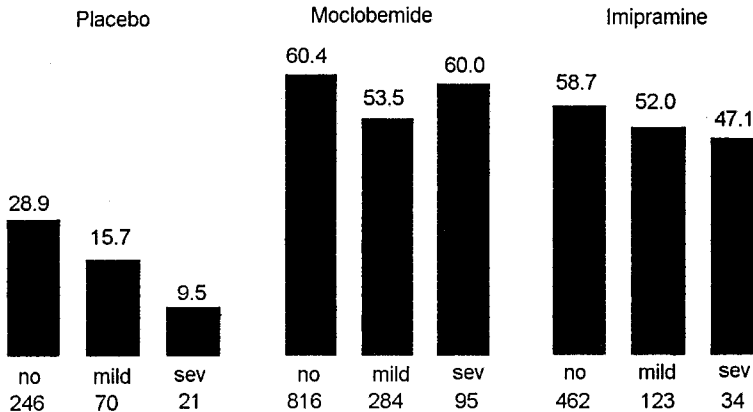


Fig. 7. Obsessive - Compulsive symptoms: Response %

In a further analysis, we investigated the action of **psychotic vs non-psychotic** depressives to moclobemide. For this analysis we defined psychotic as the manifestation of delusions and hallucinations, as assessed by the 21-item Hamilton Rating Scale, including item 20, paranoid ideation. A first analysis compared the response measured by the Hamilton Rating Scale and the Global Assessment of Efficacy. No difference in the response of psychotic vs non-psychotic patients under moclobemide or imipramine emerged, whereas the

placebo response was definitely lower in the psychotic subgroup, but still present in 10% of cases. A further analysis concentrated on the more severely affected hospitalised psychotic vs non-psychotic patients. The results were measured by the Hamilton Rating Scale and the Global Assessment of Efficacy and, again, no difference in the response to moclobemide was obtained.

To our astonishment, we failed to find a difference in response between **inpatients and outpatients**. Yet, the response to placebo met our expectations fully; the response rate was doubled in ambulatory cases, compared to hospitalised patients. The fact that no difference in the response of ambulatory vs hospitalised patients treated with the active compounds of moclobemide and imipramine was detected, has to be interpreted with cautiousness, because we cannot exclude the possibility that the most severely depressed patients in hospital did not enter the controlled study. A selection effect may be responsible for this result.

8. Predictors of Response

As already mentioned, untreated so-called drug naive patients are more suitable for drug trials and are better responders. An unsuccessful pre-treatment with tricyclic antidepressants lowers the response by about 10%. This is true for both placebo and drug treatment. The overall placebo response, for instance, was 28% in untreated patients and only 17% in pretreated patients. A similar difference was noted for moclobemide (63 vs 51) and imipramine (63 vs 53) treated patients.

A concomitant treatment with benzodiazepines improves the placebo response from 21 to 28%, as shown in fig.8. In contrast, drug treated patients undergoing comedication revealed in both cases, moclobemide and imipramine treatment, a slightly lower response than under monotherapy. The explanation for this may be that if a patient doesn't respond sufficiently to drug treatment, doctors are inclined to add a second treatment. Yet, there is another more

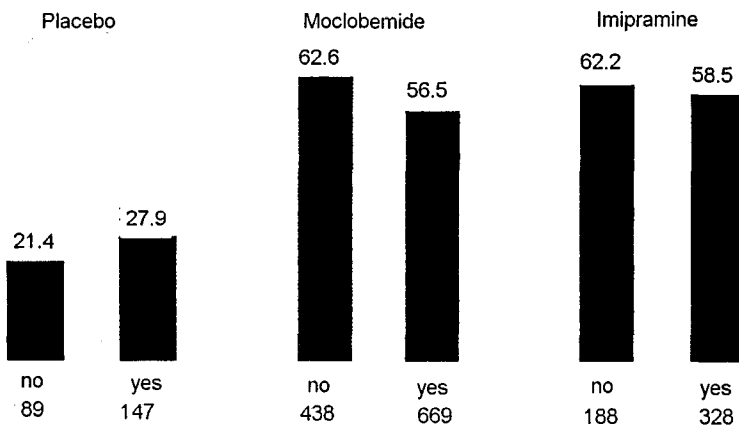


Fig. 8. Benzodiazepines co-medication: Response %

accurate explanation; patients who are treated with benzodiazepines are more often pre-treated patients and this additional medication is then maintained throughout the drug trial itself.

Another predictor of response is the previous course of the disorder. In a large open study carried out in general practice in Switzerland with 582 patients, the previous history of the illness was subclassified into first, recurrent or chronic episode. The treatment results, as assessed by the Global Clinical Improvement Scale, revealed that first episode patients responded very well to treatment, chronic episode patients poorly and the recurrent episode group took an intermediate position. A complete failure of treatment was recorded in 10% of first episode patients, 16% of recurrent episodes and 22% of chronic episode patients (Angst et al., 1993).

In this context, it is also interesting to compare the treatment results of this open study to the moclobemide results from double blind trials (Table 5). No difference at all between the outcome of the two designs is visible. This finding corresponds to our belief that a carefully planned and executed open study, under the direction of trained doctors, can yield very conclusive results.

Table 5. Meta-analysis. Response rate to placebo, double blind trials and open study with moclobemide

	Response in %				
	N	+++	++	+	0
1. Placebo	234	13	13	23	51
2. Moclobemide versus placebo	235	36	28	11	23
3. Moclobemide double blind	858	29	32	18	20
4. Moclobemide open study	654	30	34	19	18

Reference:

Angst J.; Stassen HH.: Methodische Aspekte von Studien zur antidepressiven Wirksamkeit. In: Steinberg R., Philipp M., Möller HJ. (Ed.). Spezielle Aspekte der antidepressiven Therapie. Neuere Ergebnisse zu Moclobemid. MMV Medizin Verlag GmbH, München 1994

With such a large sample of patients, we were able to determine by multivariate statistical methods, if there was an interaction with a co-medication of anti-rheumatic or cardiovascular drugs (Angst et al., 1993). In practice, many patients do not only suffer from depression, but also from physical disorders which require treatment. In the data we collected, there was no interference from anti-rheumatic or cardiovascular drugs. As already mentioned, the combination with benzodiazepines was associated with a lower response, because such patients were more chronic and more often pretreated. The same is true for higher doses given to non responders.

9. Conclusions

The efficacy of moclobemide has been well established by both placebo and comparative studies with standard tricyclic antidepressants. The response rate with moclobemide was at least twice as high as the response rate yielded under placebo. Some trials vary considerably in their outcome and the differences obtained can be due to the divergent selection of patients. A poor outcome with moclobemide, in contrast to placebo, was reported with reactive and neurotic depressives. Such differences cannot be explained by the diagnoses, but by severity. It is virtually impossible to distinguish between placebo and active antidepressants if administered to mild depressives and especially if benzodiazepines is combined with placebo. This fact has been verified by studies by Stewart et al. (1983) and Paykel et al. (1988). The high placebo response rate obtained with mild depressives considerably lowers the power of studies and the differences are also blurred if benzodiazepines is administered in conjunction with placebo.

The **onset of action** of moclobemide is usually visible within the first or second week. Two thirds of patients can become responders, as with standard tricyclic antidepressants. If no change in symptoms is observed with acute depression, in a two week treatment period when high dosages are applied, a change of medication has to be considered. With more chronic depression, i.e. dysthymia or double depression, an initial period of 4-8 weeks is necessary before an onset of action can be observed. Like most tricyclic and other heterocyclic antidepressants, moclobemide is appropriate and useful for all subgroups of depression; bipolar and unipolar depression, neurotic reactive depression, major depression, dysthymia, double depression and, above all, for elderly subjects, because of its good tolerability.

If we control for severity, no difference in the efficacy between diagnostic subgroups is present. The same is true for certain syndromes, for instance, agitation vs retardation, the presence of suicidal or obsessive compulsive symptoms, combined with depression and psychotic symptoms. The only exception up to now, has been the treatment of hospitalised psychotic and severe depressive patients. Here, clomipramine seems to be superior, whereas moclobemide is equal in response to imipramine. No difference in the response between males and females has been found, but the response is definitely better in non-pretreated so-called drug naive patients under monotherapy. Benzodiazepines does not, as a rule, increase the response rate, but may alleviate certain symptoms, for instance, insomnia. Acute first episode patients respond better to moclobemide than chronic patients, as illustrated by the results comparing double depression with dysthymia.

The good tolerability of moclobemide and the lack of any sedative side effects is a great advantage for subjects of all ages, especially the elderly. Moreover, driving ability is not impeded under moclobemide and there is no interaction with alcohol. Moclobemide is a highly recommendable drug, especially for outpatients.

I personally, consider it to be a first choice drug for all forms of depression, especially in ambulatory treatment. Classical MAO-inhibitors have been mere second or third choice treatment drugs for depression up to now and moclobemide as a reversible MAO-inhibitor should not only be administered to ambulatory patients, but also to moderate and severely depressed hospitalised patients.

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