"NEW" BETTER THAN "OLD"?

Detection of differences in efficacy between treatments in depressed inpatients under optimal conditions

"NIEUW" BETER DAN "OUD"?

Detectie van verschillen in effectiviteit tussen behandelingen bij opgenomen depressieve patiënten onder optimale condities

Jan Anthonie Bruijn

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Depression:

....There is a pitch of unhappiness so great that the goods of nature may be entirely forgotten, and all sentiment of their existence vanish from the mental field. For this extremity of pessimism to be reached something more is needed than observation of life and reflection upon death. The individual must in his own person become the prey of pathological melancholy..... Such sensitiveness and susceptibility to mental pain is a rare occurrence where the nervous constitution is entirely normal; one seldom finds it in a healthy subject even where he is the victim of the most atrocious cruelties of outward fortune... it is positive and active anguish, a sort of psychical neuralgia wholly unknown to healthy life.

William James (1968)

Aan Lieke,
Eveline, Esther en Merel
Ter nagedachtenis aan mijn ouders

Contents

1 Introduction

Chapter 1

Introduction

This thesis is concerned with the pharmacotherapy of inpatients with a major depressive disorder. In this introduction, the background of the present study is discussed, subsequently the aims of the study, and finally the structure of this thesis. The background section is divided into four parts. Firstly, epidemiological aspects of major depressive disorder are described and an attempt is made to describe the characteristic features of depressed inpatients. Secondly, the development of antidepressants is described and reports on the efficacy of antidepressants in inpatients are evaluated. Additionally, methodological aspects of these studies are evaluated to estimate the available evidence. Thirdly, several aspects of lithium addition to antidepressant treatment for unresponsive depressed patients are discussed. Finally, aspects of trait anxiety, as a possible predictor of response to treatment with antidepressants, are discussed.

Background

Epidemiological aspects of unipolar depression

Depressive disorders are common. International public health experts acknowledge the high prevalence of unipolar major depressive disorder combined with the pervasive human misery and impaired general functioning, and have identified this disorder in 1997 as the fourth most important cause of disability and premature death world wide (Murray and Lopez, 1997a). Moreover, they expect depression to become the most important cause of disability and premature death by 2020 (Murray and Lopez, 1997b). The world wide 1-year prevalence for unipolar major depression according to the DSM-III criteria (APA, 1980) ranges from 0.8% to 5.8%, while the lifetime prevalence ranges from 1.5% to 19% (Weissman et al., 1996). The 1-year prevalence of unipolar major depression for the United States ranges from 5% in the Epidemiological Catchment Area Study (Regier et al., 1993) to 10.3% in the National Co-morbidity Study (Kessler et al., 1994).

In the Netherlands, the 1-year prevalence of unipolar depression in the community is 5.8% and the lifetime prevalence is 15.4% (Netherlands Mental Health Survey and Incidence Study, NEMESIS; Bijl et al., 1997). The 1-year prevalence of depression recognised by general practitioners is 4%-5%, of depressive patients

referred to psychiatric outpatient services 0.64%, and of depressive patients referred to inpatient services 0.15% (Ormel and Sytema, 1999). The Netherlands with 15.8 million inhabitants, thus, counts 916,400 depressives in the community across each 1-year period. Of this number about 711,000 are identified as depressed by general practitioners, while about 101,120 are referred to psychiatric outpatient services of whom 23,700 (23%) per year are admitted in hospitals. Thus, a substantial percentage of all depressives stay unrecognised and, thus, untreated, while a relatively small percentage of those who are identified as depressed are treated in psychiatric services.

Little is known about factors that determine whether or not medical treatment is obtained. Also, little is known about which factors characterise depressed inpatients versus outpatients. Mendlowicz et al. (1998) found that inpatients and outpatients differed significantly in the severity of stressors, coping abilities and history of previous hospitalisations, but not in mean total scores on depression rating scales. Inpatients more often present with melancholia and a greater risk of suicide (Stage et al., 1998). Besides, inpatient populations of depressed patients have a relatively high proportion of psychotic depressed patients, of treatment resistant patients and of patients with a duration of the current episode of depression longer than one year (Bouvy, 1997).

The development of antidepressants

Since Kuhn (1958) introduced the tricyclic compound imipraminehydrochloride as an effective antidepressant, many other tricyclic antidepressants (TCAs) have been developed. Throughout the last 30 years, considerable efforts have been made to develop pharmacologically different drugs with the purpose to replace the TCAs as the primary treatment for depression. These efforts are understandable since the TCAs, although therapeutically quite efficient, pose several problems such as slow or delayed onset of action, side effects and toxicity when taken in overdose. Especially the selective serotonin re-uptake inhibitors (SSRIs) have increasingly become first choice in the treatment of depression next to the well-established TCAs, probably because of their more benign side effect profile and safety. Of the many clinical trials comparing the efficacy of antidepressants, only very few resulted in significant differences between the tested compounds in treating depression in general, as well as in treating subtypes of depression. These observations fuelled the opinion that most antidepressants are equally effective, regardless of the type of depression.

However, in spite of the many reports showing no differences in efficacy between the various antidepressants, there has also been growing concern during the past 20

years, about the evidence for therapeutic efficacy of several of the new drugs. For instance, Zis and Goodwin (1979) analysed the evidence from controlled clinical trials for the antidepressant efficacy of iprindole and mianserin. For both compounds they concluded that the existing reports on clinical trials suggested considerable methodological shortcomings in terms of design, sample size, selection criteria, duration, dose levels, etc., such that no valid conclusion concerning their antidepressant properties could be drawn. In addition, Cording-Tömmel and Von Zerssen (1982) and Kragh-Sørensen et al. (1983), applying a methodology more appropriate to detect differences, found that mianserin was virtually devoid of any antidepressant effect in endogenously depressed patients (Research Diagnostic criteria [RDC]; Spitzer et al., 1978). Subsequently, the reports of Gram et al (1983) and Guy (1986) suggested that the SSRIs are less effective antidepressants than the TCAs. These reports stressed the importance of evaluating the magnitude of the type-2 error problem studies comparing the efficacy of new antidepressants versus the TCAs. A possible difference in efficacy between the drugs may have stayed undetected as a result of methodological flaws and/or a too low statistical power. In many studies comparing a new antidepressant with a TCA, the statistical "no difference" conclusion has been taken as an indication of therapeutic equivalence with the TCA. Pocock (1985) in his book on the methodology of clinical trials calculated that a very substantial number of patients are needed to establish with any confidence that two treatments have comparable efficacy. If, for instance, a new drug treatment is compared to a standard drug treatment in a randomised trial, and if this new treatment will only be considered acceptable if it can be demonstrated with 95% confidence that the number of responders to this new treatment is at worst 10% less compared to the standard treatment, then there are at least 332 patients needed in each treatment condition. Thus, in a clinical trial comparing two treatment groups, a sample size of at least 2 x 332 = 664 patients is needed. In this case, the degree of certainty that the *a priori* defined difference, if present, would be detected is set at 1 - 0.2 = 0.8 (0.2 = type-2 error), which is called the "power" to detect a difference (in this case a difference of 10% in number of responders).

The SSRIs versus the TCAs

The existing number of studies comparing SSRIs to TCAs made it possible to perform meta-analyses to overcome the problem of small sample size and type-2 error (Tyrer, 1992). Anderson and Tomenson (1994) performed a meta-analysis comparing the efficacy of the TCAs and the SSRIs including outpatient as well as inpatient studies. This meta-analysis was reported more in detail for inpatient groups

(Anderson, 1998) and was updated recently (Anderson, 2000). Included were all randomised, controlled trials published up to May 1997, investigating the efficacy of SSRIs (fluoxetine, fluvoxamine, paroxetine, sertraline, or citalopram) against a TCA in patients with unipolar depressive illness. A total of 10,706 patients from 102 studies were included in the analyses, of which 5,533 received an SSRI and 5,173 a TCA. Subgroup analyses were performed for older versus younger, high versus low severity, and high versus low dose TCA groups. There were no significant differences in efficacy between the SSRIs and the TCAs, both in the total patient population and in these subgroups. No significant difference in efficacy between the drug classes was observed in the subgroup containing general practice and outpatients. However, in the inpatient group, TCAs were found to be significantly more effective than SSRIs.

A possible explanation for the superiority of TCAs over SSRIs in inpatients is that treatment compliance is better in inpatients than in outpatients, as nurses more closely supervise inpatients. Thus, a better compliance might reveal an existing difference between antidepressants among hospitalised patients, which remains obscure in outpatients.

However, it also is possible that this superiority of TCAs in inpatients is related to differences between outpatients and inpatients that make the latter more responsive to TCAs. These differences cannot be related to severity of depression, as measured by an initial high score on the Hamilton Rating Scale of Depression (HRSD; Hamilton, 1960), because the benefit of TCAs in this subgroup is not related to the HRSD score of the patients (Anderson, 2000), and because inpatients and outpatients do not differ in mean total scores on depression rating scales (Mendlowicz et al., 1998). Apparently, other differences do play a role. As mentioned before, inpatients more often present with melancholia, a greater risk of suicide, psychotic features, treatment resistance and a relatively long duration of the current episode of depression than outpatients (Bouvy, 1997; Stage et al., 1998). Anderson (2000) gives an alternative explanation for the difference in efficacy between SSRIs and TCAs in inpatients. He observed that clomipramine and especially amitriptyline were the most effective antidepressants in inpatients. Clomipramine and amitriptyline are so-called dual action TCAs: they inhibit both noradrenalin and serotonin re-uptake. Therefore, Anderson hypothesised that this pharmacological property makes these TCAs more effective in these inpatient studies and stated that it will be important to explore the efficacy of the newer dual action antidepressants, such as venlafaxine and mirtazapine in inpatients. However, Anderson (2000) also stated that caution is required in the interpretation of this result, as there exists no

statistically significant difference in efficacy between dual action and noradrenergic TCAs. Furthermore, his explanation does not make clear why the superiority of these dual action TCAs did not show up in outpatients.

Finally, another explanation might be measuring blood levels of the TCAs in some of the studies. Two of the three trials among inpatients that did find a significant difference between a SSRI and a TCA were trials with blood level control of clomipramine (DUAG, 1986; 1990). Another double-blind blood level controlled study (Roose et al., 1994), which was not included in this meta-analysis because it was not randomised, also showed a significant and clinically relevant difference between a TCA (nortriptyline) and a SSRI (fluoxetine). How relevant is measuring a blood level of TCAs? Dosing of TCAs without blood level control will not result in an adequate blood level of the antidepressant in 30%-50% of the patients (Perry et al., 1994; Moleman et al., 1996). In addition, flexible dosing of TCAs without blood level control is more problematic than fixed dosing because disturbing side effects could result in doses below the therapeutic level (Gram, 1990). All this may lead to response rates below the real potentials of these drugs. The majority of trials included in the meta-analysis of Anderson (2000) used a flexible dose design without blood level control. This may have lowered the efficacy of the TCAs used in these trials, which implicates that real differences between TCAs and SSRIs may have been missed. This also may have influenced the results of the meta-analysis considerably.

The newer antidepressants, pharmacologically different from SSRIs, versus the TCAs

In view of the differences in efficacy between TCAs and SSRIs in inpatients, the question of the efficacy of the newer antidepressants in inpatients is of interest. This review concerns only those newer non-SSRI antidepressants that are registered in the Netherlands: moclobemide, trazodone, nefazodone, mirtazapine and venlafaxine.

Randomised controlled trials comparing the efficacy of the newer antidepressants against a TCA in inpatients with major depressive disorder were identified by manual cross-referencing and a Medline® search up to September 2000 (search terms: drug name; randomised controlled trial; controlled trial; depression; major depressive disorder; inpatients) without language restrictions.

The search resulted in identifying 8 inpatient studies. There were no inpatient studies on nefazodone. For the 8 studies identified, sample size (power), diagnostic criteria, selection, and description of the study population, dosing design, duration of trial, dropout rate, use of concomitant psychotropic medication, outcome criteria and results are listed in Table 1. As can be seen, except for one (DUAG, 1993) showing superiority of the TCA clomipramine over moclobemide, all studies in this

Table 1. Methodological aspects of eight trials with newer antidepressants and TCAs

•Author(s) •Results •Drugs	•Diagnosis •Outcome	•Description of study population	•Sample size •Dropouts (%) •Concomitant medication	•Design •Duration of trial •(Mean) Dose mg/day
Guelfi et al., 1992 *Not significant* Moclobemide Clomipramine	DSM-III Newcastle MADRS HRSD,CGI	Endogenous* Psychotic? Suicidal? Duration of current episode? Pre-treatment?	129 Moclobemide 15/62 (24) Clomipramine 11/67 (16) Diazepam Chloral-hydrate	Flexible dose design during 6 weeks Moclobemide 462 Clomipramine 146
DUAG, 1993 Clomipramine > Moclobemide $p = 0.018$	DUAG Newcastle HRSD Bech	Endogenous* and non-endogenous Suicidal ++. Psychotic? Only duration < 1 year Pre-treatment described	115 Moclobemide 20/57 (35) Imipramine 12/58 (21) Occasional oxazepam	Fixed dose design during 6 weeks Plama drug level control Moclobemide 400 Clomipramine 150
Kellams et al., 1979 *Not significant* Trazodone Clomipramine	No diagnostic Criteria HRSD, CGI	Endogenous* Suicidal? Psychotic? Duration of current episode? Pre-treatment?	28 Trazodone 3/9 (33) Imipramine 8/10 (80) Placebo 9/9 (100) Chloral-hydrate	Flexible dose design during 4 weeks Trazodone 500 Imipramine 185
Feighner, 1980 *Not significant* Trazodone Imipramine	Feigner criteria HRSD CGI	Primary depression Suicidal? Psychotic? Melancholic? Pre-treatment? Duration of current episode?	45 Trazodone 7/17 (41) Imipramine 9/18 (50) Placebo 7/10 (70) Chloral-hydrate	Flexible dose design during 4 weeks Trazodone 313 Imipramine 160
Gershon et al., 1981 *Not significant* Trazodone Imipramine	DSM-III HRSD	Endogenous* depression Suicidal? Psychotic? Duration of current episode? Pre-treatment?	263 Trazodone 34/91(37) Imipramine 37/100 (37) Placebo 42/72 (58) Chloral-hydrate	Flexible dose design during 4 weeks Trazodone 215 to 370 Imipramine 112.5 to 190

Table 1 continues

Table 1 (continued) Methodological aspects of eight trials with newer antidepressants and TCAs

•Author(s) •Results •Drugs	•Diagnosis •Outcome	•Description of study population	•Sample size •Dropouts (%) •Concomitant medication	•Design •Duration of trial •(Mean) Dose mg/day
Zivkov et al., 1995 *Not significant* Mirtazapine Amitripyline	DSM-III RDC HRSD BPRS, GAS	} No suicidal patients } Melancholic? Psychotic? } Only duration < 6 months } No antidepressants allowed in	244 Mirta:19/133 (14) Ami: 22/111(19) Chloral-hydrate/benzo-diazepine	Flexible dose design during 6 weeks Mirtazapine 48.5 Amitriptyline 182.7
Richou et al., 1995 *Not significant* Mirtazapine Clomipramine	DSM-III RDC HRSD MADRS BPRS, GAS	} month before admittance } Pre-treatment before that } month?	174 Mirtazapine:24/87(28) Clomipramine 27/87 (31) Chloral-hydrate Benzodiazepine	Flexible dose design during 6 weeks Mirtazapine 47.3 Clomipramine 113.7
Benkert et al., 1996 *Not significant* Venlafaxine Imipramine	DSM-III-R HRSD MADRS	Suicidal? Melancholic? Psychotic? CGI: 65% moderate to markedly, 35% severely to extremely ill 85% duration < 6 months Pre-treatment?	167 Venlafaxine 21/85 (25) Imipramine 31/82 (38) Chloral-hydrate Benzodiazepine	Fixed dose design during 6 weeks Venlafaxine 365 →150 Imipramine 200

* "Endogenous" is comparable to the term "melancholic"

Diagnostic criteria and rating scales: DSM-III: Diagnostic Statistical Manual (APA, 1980); DUAG scale: Scale of the Danish University Antidepressant Group (DUAG, 1993); Feighner criteria (Feighner et al., 1972); RDC: Research Diagnostic Criteria (Spitzer et al., 1978); DSM-III-R: Diagnostic Statistical Manual, revised (APA, 1987); Newcastle scale (Roth et al., 1983); MADRS: Montgomery-Åsberg Depression Rating Scale (Montgomery and Åsberg, 1979); HRSD: Hamilton Rating Scale for Depression (Hamilton, 1969). CGI: Clinical Global Impression (Guy, 1976); Bech-scale (Bech et al., 1986); BPRS: Brief Psychiatric Rating Scale (Overall and Gorcham, 1962); GAS: Global Assessment Scale (Endicott et al., 1976)

overview failed to detect a difference between the tested antidepressants. However, as indicated by Angst et al. (1989), a number of methodological problems concerning the variables listed in Table 1 may invalidate clinical trials of antidepressants.

Sample size. The sample size of the studies ranges from 28 – 263. As discussed earlier, the sample size has to be at least 664 to take a "no difference" conclusion as an indication of therapeutic equivalence of the new drug and the reference drug, if the power is set at 0.8 (Pocock, 1985).

Diagnostic and outcome criteria. Most studies use internationally accepted diagnostic criteria except one (Kellams et al., 1979). Outcome criteria seem to be well defined and accepted rating scales are used in all studies.

Study population. The description of the study population in most studies is incomplete. None of the studies describes whether psychotic depressed patients are included. This is of interest, because psychotic depressed patients have been reported to show a weak response to treatment with antidepressants alone (Glassman et al., 1975; Parker et al., 1992; Schatzberg and Rothschild, 1992), and no antipsychotics were allowed in any of these studies. Thus, given the opinion of many authors that psychotic depressed patients need treatment with a combination of an antidepressant and an antipsychotic, it is unlikely that psychotic depressed patients are included in these studies (Spiker et al, 1985). In 2 studies patients with actively suicidal tendencies were excluded (Zivkov and De Jongh, 1995; Richou et al., 1995) and only 1 study describes inclusion of suicidal patients (DUAG, 1993); in the other 5 studies it is not explicitly mentioned. Exclusion of suicidal patients is of interest because suicidality is one of the characteristic features of inpatients (Stage et al., 1998). The same issue applies to melancholic depression. In 4 studies it is not clear which proportion of the patients had melancholic features (Feighner, 1980; Zivkov and De Jong, 1995; Richou et al., 1995 and Benkert et al., 1996). Patients with melancholic features are more often present in inpatient groups (Stage et al., 1998) and it is relevant to know their specific response to the newer antidepressants in view of their weaker response to treatment of SSRIs compared to treatment of TCAs (Perry, 1996). Another relevant patient characteristic is duration of the current episode, because there may be a substantial difference in response rates between patients with short and long lasting depressive episodes, and because, in addition to higher true response rates, higher placebo response rates are found in patients with episodes of short duration (Angst et al., 1989). In only 4 studies the duration of current episode is mentioned: DUAG (1993) excluded patients with duration of current episode longer than 12 months. Zivkov and De Jong (1995) and Richou et al. (1995) excluded patients with duration of current episode longer than 6 months. In one

study 85% of patients had a duration of current episode shorter than 6 months (Benkert et al., 1996). Additionally, it is remarkable that none of these studies describes pre-treatment during the current episode although adequate pre-treatment may be an important predictor of non-response (Bouvy, 1997). Finally, patients who have been adequately pre-treated during the same episode with one of the antidepressants investigated in a certain trial should be excluded from that trial. In only one study this exclusion criterion is mentioned (Benkert et al., 1996).

Dropout rates. High dropout rates may bias the results of a trial. Evidence-Based Mental Health states that a dropout rate higher than 20% is not acceptable (Anonymous, 2000). The higher the dropout rate, the smaller the proportion of patients completing treatment, resulting in weakening of the power of that study even when an intention to treat analysis is performed. A skewed distribution of dropouts is even more blurring, because the reason of withdrawal can be related to properties of one of the drugs (Angst et al., 1989; DUAG, 1993). In 5 studies the dropout rate is high in relation to sample size (Kellams et al., 1979; Feighner, 1980; Gershon et al., 1981; Richou et al., 1995; Benkert et al., 1996). In 2 studies the dropout distribution is skewed as a consequence of inefficacy of one of the tested antidepressants, moclobemide (Guelfi et al., 1992; DUAG, 1993).

Concomitant medication. If concomitant psychotropic medication is used, the differences in efficacy between treatment groups may be blurred (Angst et al., 1989; Angst, 1993). In all studies anxiolytic and/or hypnotic medication was used. None of the studies described the mean dose of concomitant medication that was used. In only 3 studies the exact numbers of patients which used concomitant medication in each treatment group were described (Guelfi et al., 1992; Zivkov and De Jongh, 1995; Richou et al., 1995). DUAG (1993) described the distribution of occasional use of concomitant medication between the 2 study groups. The other 4 studies reported neither the numbers of patients, who used concomitant medication, nor the distribution of this medication between the 2 treatment groups.

Dose design. There were 2 studies with a fixed dose design. At a fixed dose of 150 mg/day, clomipramine resulted in a therapeutic level in the majority of patients (DUAG, 1993). Benkert et al. (1996) also applied a fixed dose design, but without blood level control. In a study of Glassman et al. (1977) on the clinical implication of imipramine blood levels, a fixed dose of 225 mg imipramine/day resulted in a therapeutic blood level in only 60% of patients. Thus, it is unlikely that the fixed dose of 200 mg imipramine/day in the study of Benkert et al. (1996) has resulted in therapeutic levels in more than 60% of patients. There were 6 studies with a flexible dose design (Guelfi et al., 1992; Kellams et al., 1979; Feigner, 1980; Gershon et al.,

1981; Zivkov and De Jongh, 1995; Richou et al., 1995). As discussed earlier a flexible dose design can easily result in doses of the TCA below the therapeutic level.

Duration of trial. All studies fulfilled the criterion of duration of the trial of at least 4 weeks (Angst et al., 1989).

In conclusion, there are only a few randomised, controlled trials comparing the newer antidepressants moclobemide, trazodone, mirtazapine and venlafaxine to TCAs in inpatients. Only 1 study showed a significant difference between the new antidepressant versus clomipramine: moclobemide was less effective than clomipramine (DUAG, 1993). The study population was clearly described and the results seem to be generalisable to other inpatient groups with the exception of psychotic depressed patients. Patients in this study were treated in a fixed dose design with blood level drug measurements. In the other 7 studies no significant differences between the newer antidepressants and TCAs were found. However, the sample size of all of these trials in combination with a number of other methodological shortcomings make it impossible to take the "no difference" conclusion as an indication of therapeutic equivalence of the new drug and the reference drug. Moreover, in view of the study populations of these studies, it is unlikely that their results could be generalised to other inpatient groups including patients with melancholic features, with psychotic features, with substantial suicidality, with treatment resistance and with a relatively long duration of the current episode of depression. Given the low number of studies on these newer antidepressants and given the methodological weaknesses of most of these studies, the efficacy of these drugs compared to the TCAs in inpatients is still uncertain.

From this review it is clear that there is a need for more clinical trials in inpatients comparing treatment with the newer antidepressants to the established standard treatment with TCAs. Therefore, the present study comparing mirtazapine to imipramine in inpatients with major depression is relevant. Studies on mirtazapine as well as venlafaxine are of particular interest because many authors use the "dual action" properties of these drugs as an argument for choosing these drugs in (treatment resistant) inpatients (Kasper, 1997; Hirschfeld, 1999; Montgomery, 1999; Möller, 2000) despite the lack of evidence.

Lithium addition in treatment resistant depressive patients

In addition to the issue regarding the optimal antidepressant treatment, there is the question with respect to the strategy in treatment resistant depressive patients. Studies have shown, that in patients with melancholic depression treatment response

rates are 60% to 65% when blood levels of the drugs are not used to adjust the dose, and 80% to 85% when the dose of the antidepressant is adjusted on the basis of routine measurement of blood levels (Glassman et al., 1977; Reisby et al., 1977). Thus, according to these results, 15% to 20% of patients with melancholic depression is resistant to treatment.

Lithium addition appears to be an effective strategy in patients with treatment resistant depression in about 50% to 60% of cases (Schöpf, 1989; Katona et al., 1995; Austin et al., 1991; Bauer and Döpfmer, 1999). It is the treatment strategy in treatment resistant depression that has been investigated most frequently in placebo controlled double-blind studies (Bauer and Döpfmer, 1999). In several guidelines regarding treatment of major depressive disorder, lithium addition is advised in case of non-response to a single antidepressant (DeGroot, 1995; Birkenhäger and Moleman, 1998; Nolen and Hoogduin, 1998; Anderson et al., 2000; APA, 2000). From a clinical perspective, lithium addition is an attractive alternative in a non-responding depressed patient; there is considerable likelihood of response, the effect can be rapid (DeMontigny et al., 1985), and the problems associated with withdrawing an antidepressant and starting a new one may be avoided.

The treatment with an antidepressant and the addition of lithium, however, are often regarded separate, unrelated treatment decisions (Anderson et al., 2000; APA, 2000). Thus, in prescribing an antidepressant, the efficacy of possible lithium addition to that specific antidepressant is not taken into account. This may be of clinical relevance, as the efficacy of lithium addition may differ between antidepressants (Price et al., 1986). Similarly, in studies on the efficacy of lithium addition, non-responders to an antidepressant are mostly recruited without much attention for details of the treatment phase that resulted in non-response (Schöpf, 1989; Katona et al., 1995). Therefore, comparison of the overall effectiveness of treatment strategies of different antidepressants and subsequent lithium addition of the respective non-responders is of interest.

Trait anxiety as a possible predictor of response of depressive patients to specific antidepressants

Given the expanding array of effective antidepressant drugs with high response rates and with rather divergent pharmacological properties, the question of whether there are reliable predictors of response to a given drug or class of drugs is of considerable importance. To date, however, among the many possible clinical predictors which have been investigated, only a few have emerged with relative value for clinical practice (Joyce and Paykel, 1989; Goodwin, 1993): melancholic features predict a favourable response to TCAs compared to SSRIs (Perry, 1996); atypical

depressions show a better response to monoamine oxidase inhibitors compared to TCA's (Quitkin, 1990); many authors feel that psychotic features predict a poor response to a treatment with a single antidepressant without combination with an antipsychotic (Schatzberg and Rothschild, 1992). In the majority of cases, however it is still very difficult to accurately predict the response of depressed patients to medication. Predictors of response, which would be useful in identifying patients who would best be treated with a certain antidepressant, have been scarcely established (Nelson, 1999).

According to many authors major depressive disorder, although phenomenologically quite homogeneous, is aetiologically heterogeneous (Schatzberg et al., 1983; Sacchetti et al., 1987; Winokur, 1999). This may be one of the reasons that it is difficult to find clinical predictors of response to antidepressants in depressive patients. Winokur (1999) hypothesises that phenomenologically indistinguishable depressions may be separated into a group of depressions secondary to emotional instability and a group without emotional instability. According to Winokur (1999), the emotional instability in the former is caused by certain pre-existing psychiatric disorders such as anxiety disorders and personality disorders. Akiskal (1998) concludes that patients with anxiety disorders not only do develop depressions, but also that patients with high trait anxiety develop depressions. He introduced the concept of "generalised anxious temperament", indicating lifelong high trait anxiety which fluctuates in reaction to stress and which can escalate to a full-blown generalised anxiety disorder. According to Akiskal (1998), generalised anxiety disorder is in continuum with generalised anxiety temperament. This may predispose to and is often associated with depression. Janet (Jelgersma, 1939), Hays (1964), and Van Valkenburg (1983) described similar concepts. Thus, patients with a history of anxiety often develop a depression later in their life, which may be phenomenologically similar to depressions of patients without a history of anxiety.

Disorders with different aetiology may show differential response to specific treatments. Therefore, it may be useful to explore clinical, personality and biological variables which could help to distinguish patients with different levels of trait anxiety, and subsequently, to explore the predictive value of trait anxiety in depressive patients with respect to the specific response to different antidepressants.

Aims of the present study

The main purpose of this study was to compare the efficacy of mirtazapine, a new antidepressant with strong anxiolytic properties, to the efficacy of imipramine, a

standard TCA, among inpatients with a major depressive disorder, including patients with melancholic features, with psychotic features, with suicidality, with treatment resistance, and with relatively long duration of the current episode of depression. It was hypothesised that a high trait anxiety level would be predictive for response to mirtazapine, and that a low trait anxiety level would be predictive for response to imipramine in this patient group. A randomised controlled clinical trial was performed, which was designed to avoid methodological problems such as inadequate dosing of the reference drug, a high dropout rate and concomitant treatment with other psychotropic drugs. Thus, the purpose of this design was to minimise the chance of type-2 errors and to maximise the chance to observe quantitative and qualitative differences between the treatment outcomes of the two drugs.

The specific aims of this study were the following:

Primary aims: (1) To compare the efficacy of mirtazapine and imipramine in inpatients with major depressive disorder. (2) To determine the value of trait anxiety level as a predictor for response to mirtazapine and impramine, respectively.

Secondary aims: (3) To compare the efficacy of treatment of psychotic depressed patients with that of non-psychotic depressed patients in the total study population and in the mirtazapine and the imipramine group, respectively. (4) To compare the overall efficacy of 2 treatment strategies for depressed inpatients: mirtazapine and subsequently lithium addition for non-responders or imipramine and subsequently lithium addition for non-responders. (5) To determine clinical, personality and biological variables which could help to distinguish patients with different levels of trait anxiety.

Structure of the thesis

In *Chapter 2*, the pharmacological properties of mirtazapine are discussed. Subsequently, the design of the study and the selected patient population are described in detail. The results of the comparison of the efficacy of mirtazapine and the efficacy of imipramine in the total study population are given and discussed in the light of the data on this issue from the literature and in the light of the applied methodology.

In *Chapter 3*, the treatment of mood-congruent psychotic depression with imipramine is discussed. The response rate of psychotic depressed patients is compared to the response rate of non-psychotic depressed patients. Differences with

data from the literature on this issue are discussed and possible causes of these differences are evaluated.

In *Chapter 4*, the results of an analysis of different symptom clusters and their course during treatment with mirtazapine and imipramine, respectively, is reported. The implications of these results with respect to possible differences in mechanism of action between the two drugs are discussed.

In *Chapter 5*, the comparison of 2 treatment strategies for depressed inpatients is reported: mirtazapine and subsequently lithium addition for non-responders or imipramine and subsequently lithium addition for non-responders.

In *Chapter 6*, the effect of a single high dose of diazepam in depressed inpatients in relation to their trait anxiety score is discussed. Besides, the results on the relation of trait anxiety with neuroticism score, MAO activity in platelets, and response to the two drugs, respectively, are described.

In *Chapter 7*, the results of the study and clinical implications are discussed, and finally recommendations for future research are given.

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2 | A double-blind, fixed blood level study comparing mirtazapine with imipramine in depressed inpatients

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Chapter 2

A double-blind, fixed blood level study comparing mirtazapine with imipramine in depressed inpatients.

Abstract

Antidepressant effects of mirtazapine and imipramine were compared in a randomised, double-blind, fixed blood level study with inpatients in a single centre. Patients with a DSM-III-R diagnosis of major depression and a Hamilton (17-item) score of ≥ 18 were selected. After a drug-free and a placebo washout period of 7 days in total, 107 patients still fulfilling the HRSD criterion of ≥ 18, started on active treatment. The dose was adjusted to a predefined fixed blood level to avoid suboptimal dosing of imipramine. Concomitant psychotropic medication was administered only in a few cases because of intolerable anxiety or intolerable psychotic symptoms. Eight patients dropped out and 2 were excluded from analyses because of non-compliance; 97 completed the study. According to the main response criterion (50% or more reduction on the HRSD score) 11/51 (21.6%) patients responded on mirtazapine and 23/46 (50%) on imipramine after 4 weeks' treatment on the predefined blood level. Such a dramatic difference in efficacy between antidepressants has not been reported often before. The selection of (severely ill) inpatients including those with suicidal or psychotic features may have significance in this respect. Optimalisation of treatment with the reference drug imipramine through blood level control, exclusion of non-compliance for both drugs, exclusion of most concomitant medication and a low dropout rate may also have contributed. It is concluded that imipramine is superior to mirtazapine in the patient population studied.

Keywords

Mirtazapine; Imipramine; Fixed blood level monitoring; Study design; Antidepressant effect; Major Depression; Inpatients.

Introduction

Mirtazapine, a new piperazinoazepine, is a strong antagonist of central α_2-adrenoreceptors, H_1(histamine) receptors, $5HT_2$ receptors (de Boer et al., 1988) and

$5HT_3$ receptors (Kooyman et al., 1994) and a weaker antagonist of muscarine and α_1 adrenoreceptors (de Boer et al., 1988). Mirtazapine has recently been registered as an antidepressant. Efficacy and safety have been explored in controlled clinical trials (Smith et al., 1990; Claghorn and Lesem, 1995; Richou et al., 1995; Marttila et al., 1995; Van Moffaert et al., 1995; Zivkov and De Jong, 1995). In all trials tolerance and safety of mirtazapine were satisfactory. In outpatients efficacy of mirtazapine was reported to be significantly superior to placebo (Smith et al., 1990; Claghorn and Lesem, 1995) and to trazodon (Van Moffaert et al., 1995); no significant differences between mirtazapine and amitriptyline (Smith et al., 1990; Zivkov and De Jong, 1995), clomipramine (Richou et al., 1995) and doxepin (Marttila et al., 1995), respectively, have been found.

Some authors have expressed doubt whether efficacy of the "newer" antidepressants equals the efficacy of "older" antidepressants (DUAG, 1986; Bech, 1988; Potter and Rudorfer, 1989; DUAG, 1990), in spite of the fact that most clinical trials show no differences in efficacy. The methodology of such trials may not always be suitable to detect differences. Possible confounding factors involved include (Angst et al., 1989; DUAG, 1990):

1. High placebo response rates in trials without a placebo control group;
2. "Unblinding" due to different side effect profiles;
3. Treatment with sub-optimal doses of the reference drug;
4. Non-compliance and dropout, especially if not equally distributed over the different treatment groups;
5. High error variance in multicentre trials;
6. Concomitant treatment with other psychotropic drugs.

We have performed a study designed to avoid these methodological problems. The present study, comparing mirtazapine with imipramine, included:

1. A drug-free and a placebo washout period of 7 days, to exclude early placebo-responders;
2. Dose adjustment to a fixed blood level to avoid sub-optimal dosing of imipramine;
3. Allowing no concomitant psychotropic medication except in case of intolerable anxiety or intolerable psychotic symptoms;
4. No monitoring of side effects by the investigators to avoid unblinding;
5. Inclusion of inpatients only;
6. Single centre design.

Materials and methods

General outline (Figure 1)

Patients on the inpatient Depression Unit of the Department of Psychiatry of the University Hospital Rotterdam "Dijkzigt" were enrolled into the study from December 1989 to December 1993. This Unit has a regional function for treatment of uncomplicated depressed patients and a supra-regional function for treatment of therapy-resistant depressed patients. Routinely psychotropic drugs are discontinued after admission. Depressed patients were screened for inclusion and exclusion criteria. Eligible patients had to be drug-free for at least 3 days before baseline assessment. After giving written informed consent placebo was administered single blind for 4 days. At the end of this period patients were again assessed on the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960) and those still meeting inclusion criteria (HRSD ≥ 18) were randomly allocated to a double-blind treatment with either imipramine or mirtazapine. Doses of both drugs were adjusted to obtain fixed blood levels. Outcome was assessed 4 weeks after attaining these predefined blood levels.

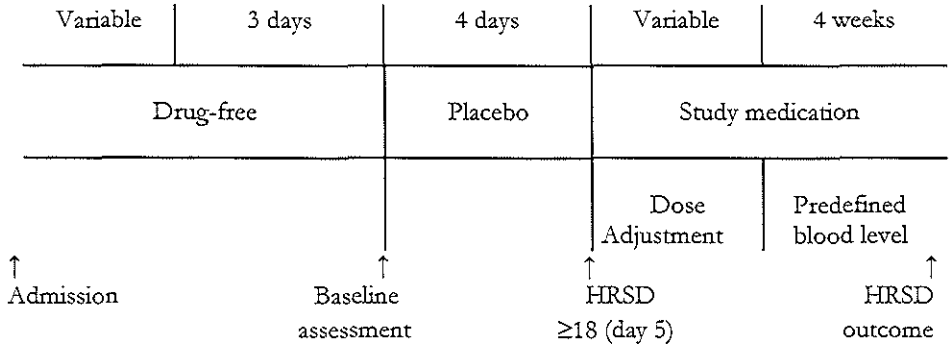

Figure 1. General outline of the study design

Patient selection

Patients were examined for inclusion and exclusion criteria before the initial placebo period and the HRSD was administered again at the end of this period. Included were patients aged 18-65 with a "major depressive episode" according to a checklist with the DSM-III-R criteria (APA, 1987) and an HRSD score ≥ 18. Excluded were patients with psychotic depression with hallucinations, schizophrenia,

paranoid psychosis, organic brain syndrome, chronic drug or alcohol abuse, clinically relevant renal, hepatic, cardiovascular, or endocrine disease, presence of absolute contraindication for either imipramine or mirtazapine, and pregnancy or the risk to become pregnant.

All assessments were done by one research psychiatrist (JB), except the SADS (Schedule for Affective Disorders and Schizophrenia; Spitzer and Endicott, 1978/79), which was performed in the presence of a second psychiatrist. In a clinical interview demographic data (age, sex, level of professional training, profession and marital status), psychiatric history (previous affective disorders, course, duration and treatment of the current episode), and family history (depression, suicide, alcohol abuse, antisocial behaviour, anxiety disorders, drug dependency and other psychiatric disorders) were obtained. The depression part of the SADS was administered at baseline by one psychiatrist in the presence of a second psychiatrist to obtain RDC diagnoses (Research Diagnostic Criteria; Spitzer et al., 1978) and to confirm the DSM-III-R diagnosis, obtained using the checklist at inclusion; scoring was based on consensus between both psychiatrists. To measure severity at baseline and response during treatment we performed 2 depression rating scales. The HRSD, which is internationally the most widely accepted depression scale, was scored at baseline (before and at the end of the placebo period) and at 2 and 4 weeks after attaining the predefined blood level of study medication. The MADRS (Montgomery-Åsberg Depression Rating Scale; Montgomery and Åsberg, 1979), which is composed of 10 depression symptoms which have proven to be most sensitive to change during treatment, was scored at baseline and weekly thereafter.

Study medication

Once a day at 10 p.m. either imipramine or mirtazapine was administered in identical capsules containing 37.5 or 75 mg of imipramine or 10 or 20 mg of mirtazapine, respectively. Treatment was started with either 75 mg imipramine or 20 mg mirtazapine. After 2 days the dose was doubled unless severe side effects were observed. Blood levels were monitored twice a week for the first 2 weeks, and weekly thereafter. The results were send to an independent psychiatrist from another ward who adjusted the number of capsules on the basis of these blood levels. The predefined blood level for imipramine + desmethylimipramine was 200-300 ng/ml (Perry et al., 1987). For mirtazapine, no therapeutic levels are known. To keep the study double-blind, to exclude treatment under extremely high or low blood levels, and to ascertain treatment compliance it was decided to adjust mirtazapine doses to blood levels around the mean levels obtained with 60 mg mirtazapine per day. This

dosage was advised at the time the study started by Organon for treatment of depressed patients. To obtain such levels we performed a pilot study in 20 patients with a dose of 60 mg. The mean steady-state blood levels in this pilot study were 67.0 ng/ml (SD ± 25.4, range 33.0-123.9). On basis of these results, predefined blood levels of 50-100 ng/ml of mirtazapine were chosen. The difference with predefined imipramine levels is, however, that optimal efficacy is not proven at these predefined mirtazapine levels.

Side effects were not systematically rated by the investigators, to prevent highlighting the different side effect profiles and, thus, introducing a bias towards "unblinding". Side effects were observed by treating psychiatrists and nurses not involved in the ratings for the study. Only in some dropout patients, specific treatment for side effects was necessary according to these observations.

Evaluation of blindness. After completion of the study the research psychiatrist (JB) guessed the medication each of the 107 patients had received. This was correct in 46 cases and incorrect in 37 cases. In 24 cases the research psychiatrist was not able to decide on 1 of the 2 study medications.

Assay of study medication. Imipramine and desipramine assays were carried out with HPLC. Mirtazapine was assayed according to Paanakker and Van Hal (1987).

Concurrent medication

Drugs for somatic complaints not interfering with study medication were continued unchanged during the study, if necessary. No psychotropic medication besides the study medication was allowed except for 1-6 tablets a day containing 45 mg of an extract of valerian in case of anxiety or insomnia. This extract was assumed to be without antidepressant effect. In exceptional cases lorazepam, 1-5 mg a day for intolerable agitation or anxiety, or haloperidol, 1-15 mg a day in case of intolerable psychotic symptoms, respectively, had been prescribed.

Data-analysis and statistical methods

The main response criterion was defined *a priori* as a reduction of 50% or more of the HRSD score 4 weeks after attaining the predefined blood level. The χ^2-test was used for comparing outcome scores between the 2 treatment groups; the *t*-test for comparing continuous outcome variables. In order to increase precision of the estimated treatment effects, ANCOVA's, using multiple linear regression analyses, were also *a priori* planned for comparing the MADRS and HRSD post-treatment scores between the 2 treatment groups with the following co-variables potentially taken into account: MADRS and HRSD pre-treatment scores (baseline severity),

duration of the present episode, number of previous depressions, manic episodes, personality, family history, previous treatments during current episode, melancholic type, psychotic features and type of depression according to RDC criteria. Adequate pre-treatment during the current episode was defined as an adequate dose of an antidepressant during at least 4 weeks (Potter and Rudorfer, 1989).

The difference in time-trend of the MADRS during 6 weeks of treatment between the 2 treatment groups was tested in a random coefficient model using rm-ANOVA.

Because efficacy of antidepressants may be less in the subgroup of psychotic patients, separate analysis of this subgroup was planned *a priori*.

Ethical considerations

The protocol was approved by the Ethics Committee of the University Hospital Rotterdam "Dijkzigt" and the Medical Faculty of the University of Rotterdam and was carried out in accordance with the ethical standards laid down in the declaration of Helsinki.

Results

Patient population and drop-outs

One hundred and seven depressed inpatients were randomised to either mirtazapine (n = 54) or imipramine (n = 53) (Table 1). Eight patients dropped out, while 2 patients were excluded from analyses because monitoring of blood levels showed non-compliance (Table 2). Five dropouts on imipramine were due to side effects, compared to none on mirtazapine. Thus, 97 patients (51 taking mirtazapine and 46 taking imipramine) completed the study.

Blood levels and doses

The mean time to reach the predefined blood levels was 10.9 days (SD ± 3.5, range 5-21) for mirtazapine and 13.6 days (SD ± 4.6, range 7-25) for imipramine. Including the 4-week treatment on this blood level, the mean total period on study medication was 38.9 days (SD ± 3.5, range 33-49) for mirtazapine and 41.6 days (SD ± 4.6, range 35-53) for imipramine. The mean daily dose during the 4 weeks on the predefined blood level for mirtazapine was 76.2 mg (SD ± 17.6, range 40-100) with a mean blood level of 69.3 ng/ml (SD ± 10.0, range 48.8-92.8), and for imipramine 235.5 mg (SD ± 90.8, range 37.5-450) with a mean blood level of imipramine + desmethyl-imipramine of 267.1 ng/ml (SD ± 35.9, range 199.0-400.3). Within this

Table 1. Total population (n = 107)

	Mirtazepine (n = 54)	Imipramine (n = 53)
Age: mean ± SD (range)	45 ± 11 (23-64)	47 ± 10 (27-65)
Sex: male/female	12/42	11/42
Diagnosis: "major depressive episode" (DSM-III-R)	54	53
**Unipolar*	49	52
Non-psychotic, 1st episode	19	23
Non-psychotic, recurrent	15	14
Psychotic, 1st episode	9	10
Psychotic, recurrent	6	5
**Bipolar*	5	1
Non-psychotic	4	1
Psychotic	1	0
Melancholic type	47	45
Major Depressive episode (RDC)	54	52
Retarded Depression (RDC)	16	16
Agitated Depression (RDC)	16	19
Endogenous Depression (RDC)	53	50
Suicidal	28	32
HRSD baseline	26.1 ± 4.5 (19-37)	26.5 ± 5.0 (18-37)
MADRS baseline	37.5 ± 6.0 (25-51)	36.2 ± 6.8 (16-54)
Duration current episode		
< 1 year	34	32
> 1 year	20	21
Adequate pre-treatment with antidepressants	28	27
Family history (1st/2nd degree)		
Depression	28	33
Suicide	10	9
Personality disorder	11	7

sum the mean blood level of imipramine was 119.13 ng/l (SD ± 44.48, range 44.6-235.0) and the mean desmethyl-imipramine was 148.01 ng/l (SD ± 54.6, range 45.0-310.3).

Table 2. Drop-outs and non-completers by non-compliance ($n = 10$)

Treatment	Reason	Day of study medication	Day after attaining predefined blood level
Mirtazapine	1. Transfer to other ward	14	-
	2. Refuse to take medication	12	-
	3. Non-compliance (blood level ↓)	31	14
Imipramine	4. Mania	18	4
	5. Orthostasis	9	-
	6. Deterioration	19	2
	7. Fever and delirium	12	2
	8. Allergic reaction	21	7
	9. Allergic reaction	36	22
	10. Non-compliance (blood level ↓)	28	7

Concomitant medication

Nine mirtazapine and 7 imipramine patients were treated with the valerian extract. There were no significant differences between the 2 treatment groups with respect to dose and duration of valerian medication. Lorazepam was administered to 6 patients (4 taking mirtazapine and 2 taking imipramine), which has been ignored in the analyses because of the small number of patients (6/107). Nine of the 31 psychotic patients were treated with haloperidol, 7 taking mirtazapine and 2 taking imipramine. Only 1 of those patients (taking mirtazapine) was a responder; the other 8 patients were non-responders. This indicates, that haloperidol was not instrumental in the recovery in those patients.

Treatment effects

According to the main response criterion, 11/51 (21.6%) patients were responders on mirtazapine and 23/46 (50%) on imipramine; a significant difference ($\chi^2 = 7.38$; $df = 1$; $p = 0.007$). In addition, the mean HRSD score after 4 weeks of predefined blood levels (Table 3) of the imipramine group was significantly lower than that of the mirtazapine group (mean difference = 5.1; SE = 1.8; $t = 2.83$; $df =$

95; $p = 0.006$). "Intent to treat" analysis ($n = 107$) with the last HRSD score carried forward showed 11/54 (20.4%) responders with the mirtazapine and 23/53 (43.4%) with the imipramine group ($\chi^2 = 5.5$; $df = 1$; $p = 0.019$).

Table 3 Mean HRSD scores at baseline and endpoint (after 4 weeks of predefined blood level)

	Intention to treat		Completers	
	Mirtazapine ($n = 53$)	Imipramine ($n = 54$)	Mirtazapine ($n = 46$)	Imipramine ($n = 51$)
Baseline HRSD	26.1 ± 4.5	26.5 ± 5.0	26.1 ± 4.4	26.7 ± 4.9
Endpoint HRSD	19.6 ± 8.7	15.8 ± 9.6	19.2 ± 8.6	14.1 ± 9.0

Since 9 of the 31 psychotic patients were treated with haloperidol and since more patients on mirtazapine received haloperidol, we have analysed the results omitting patients receiving haloperidol. The response on imipramine: 23/44 (52.3%), differed significantly from the response on mirtazapine: 10/44 (22.7%) ($\chi^2 = 6.7$; $df = 1$; $p = 0.008$).

Figure 2A (completers) and 2B (ITT with LOCF) show the mean MADRS scores for the 2 groups during 6 weeks of treatment. According to the rm-ANOVA the time-trends were significantly different between the 2 treatment groups (completers: $P = 0.003$; ITT: $P = 0.026$). Regression analyses with severity (HRSD score at baseline), suicidal or psychotic features (DSM-III-R), duration of current episode, previous adequate treatment of current episode with imipramine, with other classical tricyclics or with modern antidepressants, number of psychiatric admissions before the current depression, positive family history for depression and/or suicide, and personality disorder as co-variables did not improve the precision of the estimated difference between the 2 drugs to an appreciable extent.

In the subgroup of 31 psychotic patients 4 dropped out (2 patients taking mirtazapine and 2 taking imipramine), so 27 psychotic patients completed the study. According to the main response criterion, 4/14 (28.6%) responded on mirtazapine and 9/13 (69.2%) on imipramine ($\chi^2 = 2.98$; $df = 1$; $p = 0.084$). The mean HRSD scores after 4 weeks of predefined blood levels were significantly lower for the

imipramine group than for the mirtazapine group (mean difference = 9.8; SE = 3.8; t = 2.56; df = 25; p = 0.017). "Intent to treat" analysis in the subgroup of 31 psychotic patients showed 4/16 (25%) responders with the mirtazapine and 9/15 (60%) with the imipramine group (χ^2 = 2.59; df = 1; p = 0.11). If patients treated with haloperidol were regarded as dropouts, an "intent to treat" analysis showed the following results: 3/16 (18.8%) responders with the mirtazapine group and 9/15 (60%) with the imipramine group. This is a significant difference (χ^2 = 3.95; df = 1; p = 0.046). Figure 3A (completers) and Figure 3B (ITT with LOCF) show the MADRS scores for the 2 groups of psychotic patients during 6 weeks of treatment. According to the rm-ANOVA the time-trends were significantly different between the two treatment groups (completers: p = 0.001; ITT: p = 0.019).

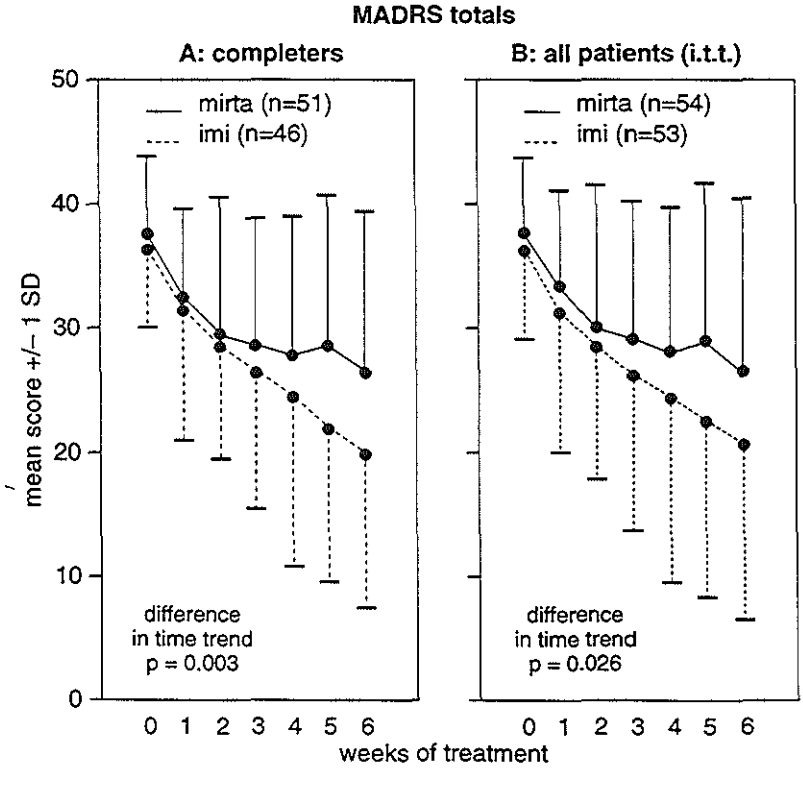

Figure 2A, B Mean total scores on the Montgomery-Åsberg depression rating scale. **A** Completers (n = 97); **B** all patients (n = 108, LOCF)

The overall response rate to treatment was rather low (50% on imipramine and 22% on mirtazapine). For this reason we performed subgroup analyses. Excluding patients with duration of the depression longer than 1 year, the response rate on imipramine was 63.3% (19/30) and 31.3% (10/32) on mirtazapine. Excluding in this subgroup also patients with adequate pre-treatment of the current episode, response rates were even higher: 69.6% (16/23) on imipramine and 37.5% (9/24) on mirtazapine. These differences between the imipramine and mirtazapine group are not significant, most likely because of the low number of patients.

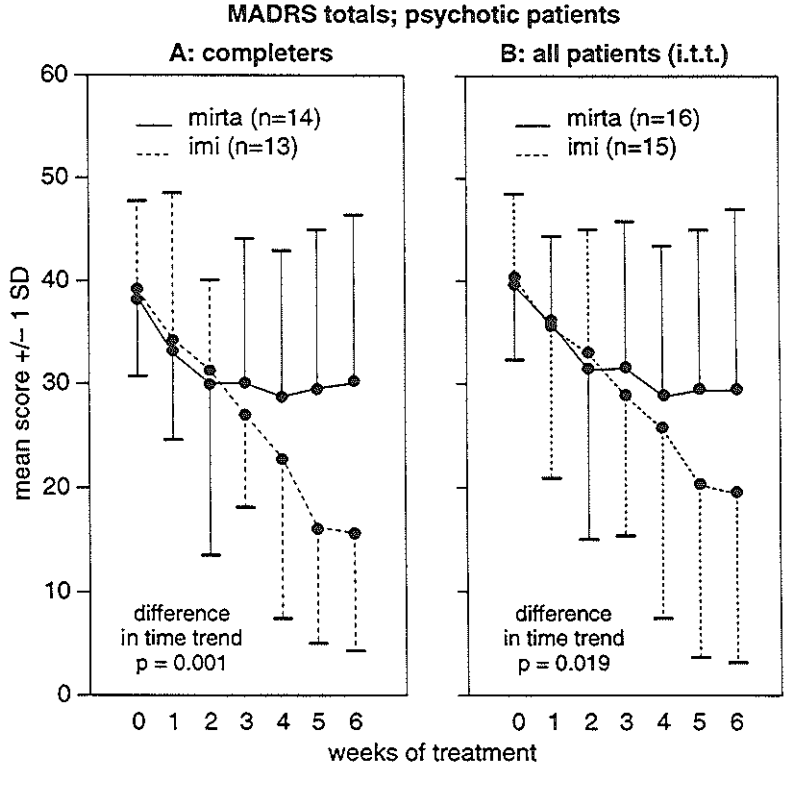

Figure 3A, B Mean total score on the Montgomery-Åsberg depression rating scale of the psychotic patients.
A Completers (n = 27); **B** all psychotic patients (n = 31, LOCF).

Discussion

The most obvious result in this study is the considerable difference in antidepressant efficacy between mirtazapine and imipramine. Such a difference has not been reported in previous studies (Smith et al., 1990; Claghorn and Lesem, 1995; Richou et al., 1995; Marttila et al., 1995; Van Moffaert et al., 1995; Zivkov and De Jong, 1995). A possible explanation may be found in differences between the present and other trials with mirtazapine.

Previous studies on mirtazapine (Smith et al., 1990; Claghorn and Lesem, 1995; Richou et al., 1995; Marttila et al., 1995; Van Moffaert et al., 1995; Zivkov and De Jong, 1995) used a flexible dose design. This may lead to inappropriate dosing especially with tricyclic antidepressants because side effects preventing dose increments may occur at sub-therapeutic doses/blood levels (Dawling, 1982; DUAG, 1990). In at least 2 previous studies (Smith et al., 1990; Richou et al., 1995) the mean dose of the tricyclic reference drug was rather low; 111 mg amitriptyline and 113.7 mg clomipramine, respectively. In the present patient group the mean daily dose of imipramine was 235.5 mg with a very wide range (37.5-450 mg). No fewer than 9 (20%) patients were on a dose of 112.5 mg or less, and 17 (37%) patients received 300 mg imipramine per day or more. This illustrates the range of doses necessary to obtain therapeutic blood levels. It is not very likely that such doses would have been administered without blood level control. With mirtazapine it was not possible to predefine an optimal blood level because therapeutic blood levels of mirtazapine are not available. The mean mirtazapine dose of 76 mg/day was above the dose used in other studies: 53 mg/day (Zivkov and De Jong, 1995) and 47 mg/day (Richou et al., 1995) in other inpatient studies. The predefined blood level of mirtazapine was based on steady-state blood levels of patients on 60 mg/day of mirtazapine, which was the recommended dose in the previous inpatient mirtazapine studies (Richou et al., 1995; Van Moffaert et al., 1995; Zivkov and De Jong, 1995).

It cannot be excluded that mirtazapine has a curvilinear blood level response curve, as is the case with nortriptyline (Perry et al., 1987), and that the present dose was less effective for that reason. Dose finding or blood level response studies to clarify this point are not available. Thus, the imipramine dose in the present study was in the therapeutic range for all patients, but this is not certain for all patients on mirtazapine, which could be one explanation for the difference in efficacy between both drugs in this study.

In the present study only a minority of patients was treated with co-medication, and the difference in efficacy between imipramine and mirtazapine remained significant if these patients were excluded. In the earlier mirtazapine studies (Smith et

al., 1990; Claghorn and Lesem, 1995; Richou et al., 1995; Marttila et al., 1995; Van Moffaert et al., 1995; Zivkov and de Jong, 1995) short acting benzodiazepines were allowed for the first 2 weeks and chloral hydrate (0.5-3 gr) during the entire study. It was not reported whether the co-medication was equally divided between the 2 treatment groups. Angst (1993) has argued that co-medication with benzodiazepines increases response to placebo treatment and decreases the power of a comparative trial considerably. It may be of significance, therefore, that other studies with mirtazapine reported response percentages as high as 72% (Zivkov and de Jong, 1995), 80% (Richou et al., 1995), and 78% (Van Moffaert et al., 1995), respectively.

The dropout rate in the present study was low: 9.1% versus 17-35% in other mirtazapine studies (Smith et al., 1990; Claghorn and Lesem, 1995; Marttila et al., 1995; Van Moffaert et al., 1995; Richou et al., 1995; Zivkov and De Jong, 1995). A high dropout rate may bias results of clinical trials even if analyses are based on "intent to treat" samples (Angst et al., 1989).

Patient selection may also play an important role in treatment outcome (Ansseau, 1992). Similar to the present trial, 3 trials of mirtazapine were performed with inpatients, comparing it with amitriptyline, clomipramine, and trazodone, respectively (Richou et al., 1995; Van Moffaert et al., 1995; Zivkov and De Jong, 1995). However, other selection criteria differed. Patients with active suicidal tendencies were excluded (Smith et al., 1990; Claghorn and Lesem, 1995; Richou et al., 1995; Marttila et al., 1995; Van Moffaert et al., 1995; Zivkov and de Jong, 1995). It is not clear whether patients with psychotic depressions and patients with a "melancholic type"-depression had been included in these studies. In the present study 29% (31/107) of the patients had psychotic depressions and 86% (92/107) fulfilled criteria for melancholic type, respectively. Outpatients (Smith et al., 1990; Claghorn and Lesem, 1995) or in and outpatients (Marttila et al., 1995) were studied in some trials, while in the 3 trials with inpatients (Richou et al., 1995; Van Moffaert et al., 1995; Zivkov and De Jong, 1995) those with a duration of the depression longer than 6 months were excluded. In 3 studies (Richou et al., 1995; Marttila et al., 1995; Van Moffaert et al., 1995) none of the patients had been treated with an adequate dose of an antidepressant in the month preceding the trial.

The present results are in some respects comparable to those of the DUAG-studies (DUAG, 1986; DUAG, 1990), in which the serotonine re-uptake inhibitors citalopram and paroxetine, respectively, were compared with clomipramine. Differences in favour of clomipramine were reported in both studies. The authors suggested that this may be related to inclusion of only inpatients, rigid adherence to a fixed dose schedule and control of drug compliance by blood level monitoring.

The subgroup of psychotic patients showed an even larger superiority of imipramine over mirtazapine, response percentages being around 60-70% for imipramine and around 20-30% for mirtazapine, depending on the analysis performed. Most of these results were significant, even with the small number of psychotic patients studied. Seven patients treated with haloperidol were taking mirtazapine and only 2 were taking imipramine, also hinting at a better efficacy of imipramine. Thus, the inclusion of psychotic patients may have contributed to the superiority of imipramine.

The response rate in this study was relatively low; 50% on imipramine compared to 70-80% in other studies (Potter and Rudorfer, 1989). This is probably due, at least in part, to a lower response rate of patients with a current depressive episode of long duration and of patients that had been pre-treated with antidepressants, since with the exclusion of these patients, the response rate was 70% (16/23) on imipramine.

In conclusion, the present study shows a considerable difference in antidepressant efficacy between the new antidepressant mirtazapine and imipramine. Optimalisation of treatment with the reference drug imipramine through blood level control, exclusion of non-compliance for both drugs, exclusion of most concomitant medication and a very low dropout rate may have contributed to this result. Also, the selection of severely ill inpatients, including those with suicidal or psychotic features, may be significant in this respect, although it is difficult to ascertain differences between patient characteristics in different studies. In the patient population studied imipramine is superior in efficacy to mirtazapine.

Acknowledgement

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3 | Treatment of mood-congruent psychotic depression with imipramine

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Chapter 3

Treatment of mood-congruent psychotic depression with imipramine

Abstract

Most studies report a poor response of psychotic depressed patients to tricyclic antidepressants in comparison with non-psychotic depressed patients and in comparison with treatment with tricyclic antidepressants in combination with antipsychotics. However, the issue of optimal treatment of psychotic depressed patients has not been resolved as yet. Previously, we reported a significant difference in response to mirtazapine compared to imipramine in a randomised, double-blind, fixed blood level study with inpatients with major depression. In the current study we focus on the response to imipramine in a group of patients with psychotic depression and compare this to patients without psychotic features. Our aim in presenting these findings was to contribute to the discussion on the optimal treatment of psychotic depressed patients. Fifty two patients with a unipolar major depression (DSM-III-R), comprising 15 patients with mood-congruent psychotic features and 37 with no psychotic features, were commenced on treatment with imipramine. The dose was adjusted to a predetermined blood level. After 4 weeks of treatment on predetermined blood level, there were 45 completers, 9/13 (69.2%) psychotic and 14/32 (43.8%) non-psychotic patients were responders. The patients with psychotic features demonstrated a lower mean final HRSD score, together with a greater fall in MADRS score over time, compared to the non-psychotic group. In this group of patients with mood-congruent psychotic depression, imipramine used on its own together with strict control of blood drug levels produced a high treatment response rate of 70%.

Keywords:

Imipramine; Fixed blood level monitoring; Study design; Antidepressant effect; Major depression with psychotic features.

Introduction

As reviewed by Schatzberg and Rothschild (1992) most studies report that depressed patients with psychotic features respond poorly to treatment with an antidepressant alone. However, the question of which treatment is optimal for patients diagnosed with psychotic depression remains as yet unresolved. In a meta-analysis of 44 studies looking at physical treatments for psychotic depression (Parker et al., 1992) combination therapy of tricyclic and antipsychotic drugs ranked as more effective than antidepressant therapy alone, but the difference was not statistically significant. The authors conclude that there is a need to re-examine the widely held view that combination therapy with an antipsychotic drug and an antidepressant preparation is superior to treatment with an antidepressant alone. One factor that may affect treatment results (the conclusions reached by research on this subject) is that diagnostic criteria for psychotic depression frequently differ from study to study. Maj et al. (1990) suggested that the inclusion in some studies of depressed patients with psychotic features that were mood-incongruent could account in part for the differences in treatment response observed between psychotic depressed patients and depressed patients without psychotic features. A second factor that may exert an important influence on results is the dose and duration of drug treatment. Quitkin et al. (1978) reported that the presence of delusions did not predict a poor response to imipramine provided that patients were treated with adequate doses for a sufficient period of time. Glassman et al. (1975, 1977), however, reported a poor response to 4 weeks of treatment with a fixed dose of imipramine in depressed patients when psychotic features were present. The one available double-blind study (Spiker et al., 1985) found the combination of amitriptyline and perphenazine clearly superior to amitriptyline alone.

The present paper forms part of a double-blind study comparing mirtazapine and imipramine in a group of depressed inpatients. The results of this comparative trial have been reported elsewhere (Bruijn et al., 1996) and indicated a considerable difference in efficacy in favour of imipramine over mirtazapine for depressed patients both with and without psychotic features. In the current study, we focus on the treatment response to imipramine in a group of patients with psychotic depression and compare this to patients who manifest no psychotic features. Our aim in presenting these findings is to contribute to the discussion on the optimal management for this patient group.

Methods

General outline

For a detailed description of the study the reader is referred to our previous report (Bruijn et al., 1996). The general outline is shown in Figure 1. Eligible patients had to be drug-free for at least 3 days before baseline assessment. Included were patients aged 18-65 with a DSM-III-R diagnosis "major depressive episode" (American Psychiatric Association, 1987) and a Hamilton Rating Scale for Depression score ≥ 18 (HRSD; Hamilton, 1960). Excluded were patients with visual hallucinations, schizophrenia, paranoid psychosis, organic brain syndrome, chronic drug or alcohol abuse, and clinically relevant somatic disease. Patients were given a detailed outline of the study, following which written consent was obtained and a single-blind placebo was administered for 4 days. At the end of this period of placebo treatment, patients were assessed again on the HRSD and those still meeting the inclusion criteria including a HRSD ≥ 18 were randomly allocated to double-blind treatment with either imipramine or mirtazapine.

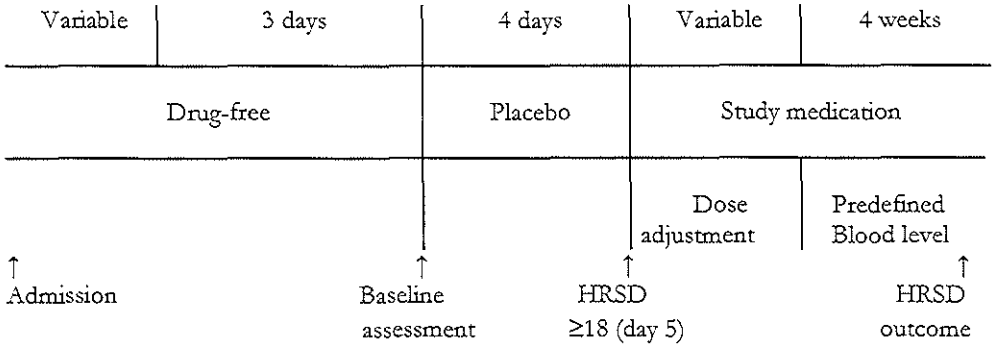

Figure 1. General outline of the study design

Blood levels were monitored at weekly intervals. Dosing was adjusted for all subjects to obtain a predetermined blood level of imipramine plus desmethyl-imipramine, of 200-300 μg/l. All assessments were done by one research psychiatrist (JB), except for the section of the Schedule for Affective Disorders and

Schizophrenia (SADS; Spitzer and Endicott, 1978/79) which relates to depression, which was performed in the presence of a second psychiatrist. This standardised interview was administered at the start of the trial to obtain Research Diagnostic Criteria (RDC; Spitzer et al., 1978) diagnoses and scoring was based on a consensus between both psychiatrists. Psychotic features were assessed during this interview. Extreme feelings of hopelessness and worthlessness were not by themselves considered sufficient for inclusion within the psychotic group. A diagnosis of psychotic depression was made only when the subject was found to be suffering from definite mood-congruent delusions as defined by the SADS. Two depression rating scales were used: the Hamilton Rating Scale for Depression, (HRSD; Hamilton, 1960) and the Montgomery Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979). Both the HRSD and MADRS were performed at the start of the study to record a baseline depression score. Thereafter, the HRSD was scored at 2 and 4 weeks after attaining the predefined blood level of imipramine and desmethyl-imipramine; and the MADRS at weekly intervals. No concurrent psychotropic medication was allowed except up to 6, 45 mg tablets of valerian per 24-hour period in the case of anxiety or insomnia. This extract was assumed to be without antidepressant effect. In 3 exceptional cases other co-medications were administered (see Results).

Data analysis and statistical methods

Response was defined *a priori* as a reduction of 50% or more of the HRSD score from baseline measurement at the start of the study to the endpoint, at 4 weeks post attaining the predetermined blood imipramine level. Patients with an outcome HRSD score of less than 10 were determined for the purposes of this study to be "in remission". The χ^2-test was used for comparing categorical variables; 95% confidence intervals are also reported. The Kolmogorov-Smirnov goodness of fit test was performed on all continuous variables to measure deviation from the curve of normal distribution. Variables which showed an approximate normal distribution were examined using independent samples *t*-tests; otherwise, Mann-Whitney tests were performed.

Since this analysis is post-hoc, it can be regarded as an observational study. Therefore, we controlled for all currently acknowledged possible confounding factors relating to the efficacy of antidepressants that may have had an impact on the difference in endpoint HRSD scores between the non-psychotic and psychotic

groups of patients (Kocsis et al., 1990; Scott, 1994). These factors were: age, duration, and severity (taken as baseline HRSD score) of present episode, psychomotor retardation, number of previous episodes of depression, and family history of affective disorder. Thus, we performed an ANCOVA using a multiple linear regression analysis: with the outcome HRSD score as the dependent variable, the presence of psychotic symptoms as the independent variable and the aforementioned possible confounding factors as co-variables. A p value < 0.05 (two sided) was considered statistically significant.

The MADRS score over time was measured at weekly intervals during 6 weeks of treatment. The difference in time-trend of this score between the 2 groups of subjects was tested in a random coefficient model using rm-ANOVA (mixed model ANOVA, using SAS statistical software package). The previously mentioned co-variables and their effects on the time-trend were again taken into account. Hence, the difference in time-trend of the MADRS score between psychotic and non-psychotic patients is adjusted for the possibly confounding effects of the above mentioned factors on the time-trend.

Ethical considerations

The protocol was approved by the Ethics Committee of the "Dijkzigt" University Hospital Rotterdam and the Medical Faculty of the University of Rotterdam and has been carried out in accordance with the ethical standards laid down in the declaration of Helsinki.

Results

Patient population, attrition and concomitant medication

Of the total of 107 depressed in-patients entered into the study, 53 were randomised to imipramine treatment. Of these, 15 were diagnosed with psychotic depression.

There were significant differences between the psychotic and non-psychotic groups of patients regarding sex, frequency of RDC diagnosis "retarded depression", total mean HRSD and mean MADRS scores at baseline, and the HRSD items "feelings of guilt", "somatic anxiety", and "insight". The difference between the 2 groups regarding the HRSD items "depressed mood", "work and activities" and "hypochondriasis" (Table 1A and 1B) was found to be just below levels of

Table 1A. Total population (n = 53); Patient characteristics

	Psychotic (n = 15)	%	Non-psychotic (n = 38)	%	Sign.p
Age: Mean ± SD (range)	49 ± 10 (34-65)		48 ± 11 (27-65)		0.57
Sex: Male	7	47	4	10	**0.007**
Female	8	53	34	90	
Diagnosis: "major depressive episode" (DSM-III-R)	15	100	38	100	
Unipolar	15		37		1.00
1st episode	10	67	23	60	1.00
Recurrent	5	33	14	37	
Bipolar	0		1	3	1.00
Melancholic type	13	87	32	84	1.00
Major Depressive episode (RDC)	15	100	37	97	1.00
Retarded Depression (RDC)	8	53	8	21	**0.04**
Agitated Depression (RDC)	6	40	13	34	0.76
Endogenous Depression (RDC)	15	100	35	92	0.55
Suicidal	7	47	25	66	0.23
HRSD baseline	29.1 ± 5 (22-37)		25.5 ± 5 (18-37)		**0.02**
MADRS baseline	39.6 ± 8 (27-54)		35.0 ± 6 (16-47)		**0.03**
Duration current episode					
< 1 year	11	73	21	55	0.35
> 1 year	4	27	17	45	
Family history (1st/2nd degree)					
Depression	10	67	23	61	0.76
Suicide	2	13	7	18	1.00
Adequate pre-treatment[1]	5	33	17	45	0.54

[1] Pre-treatment of present episode with an adequate dose of an antidepressant drug during at least four weeks (Potter and Rudorfer, 1989)

Table 1B. Total population (n = 53); HRSD items

Factor	Psychotic (n = 15) mean (range)	Non-psychotic (n = 38) mean (range)	Sign. p
Depressed mood	3.47 (3-4)	3.03 (2-4)	0.05
Feelings of guilt	2.80 (0-4)	1.42 (0-4)	**0.004**
Suicide	1.73 (0-4)	1.63 (0-4)	0.87
Insomnia early	1.60 (0-2)	1.66 (0-2)	0.80
Insomnia middle	1.73 (1-2)	1.74 (0-2)	0.75
Insomnia late	1.67 (0-2)	1.71 (0-2)	0.99
Work and activities	2.80 (2-4)	2.39 (2-4)	0.05
Retardation	1.07 (0-3)	0.61 (0-2)	0.16
Agitation	0.93 (0-3)	1.13 (0-3)	0.50
Anxiety, psychic	1.93 (0-3)	2.24 (0-4)	0.16
Anxiety, somatic	1.20 (0-2)	1.89 (0-3)	**0.006**
Somatic symptoms Gastro-intestinal	1.40 (0-2)	1.16 (0-2)	0.20
Somatic symptoms General	1.27 (0-2)	1.34 (0-2)	0.66
Genital symptoms	1.73 (0-2)	1.79 (0-2)	0.58
Hypochondriasis	1.33 (0-4)	0.58 (0-3)	0.07
Loss of weight	1.00 (0-2)	0.92 (0-2)	0.77
Insight	1.40 (0-2)	0.26 (0-2)	**<.000**
HRSD total score	29.07 (22-37)	25.50 (18-37)	**0.02**

Table 2. Delusional symptoms of psychotic patients (n = 15)

Case#/ Age/Sex	Delusional symptoms as actually reported by the patient	Delusions according to SADS score		
		Guilt/Sin	Persecutory	Somatic
1 /53/m	Is a criminal, is not worth to live, is a sinner, does not deserve to drink or to eat, has always played a game	Definite	Absent	Absent
2 /45/m	Goes to hell, is guilty of a lot of sins, deserves punishment, is being eavesdropped, does not trust anyone, is convinced that we read his mind and know everything of him.	Definite	Definite	Absent
3 /37/f	Everything around her goes wrong and it is her fault; has smashed everybody, feels a dirty lazy pig; we play a game and know everything already, we laugh at her and cut her up	Definite	Suspect or likely	Absent
4 /34/f	Is a bad christian; it is all her fault; wants to give herself up to the police, deserves a lifelong sentence, is being eavesdropped	Definite	Suspect or likely	Absent
5 /62/m	Deserves death, caused the death of another patient, is in a concentration camp, suspects a conspiracy against himself	Definite	Definite	Absent
6 /38/f	Is ugly, is already dead, has no stomach, no heart anymore, is an evil person, deserves no food and no visitors	Definite	Absent	Suspect or likely
7 /49/f	Cannot do anything anymore, is already dead, is in prison eternally; her brain is irreparably damaged, her limbs melt	Absent	Absent	Definite
8 /51/f	Has no money anymore, has ruined her family, deserves punishment, is already dead, has no heartbeat anymore, cannot do anything and knows nothing anymore	Definite	Suspect or likely	Definite
9 /64/m	Has cancer and aids, is a piece if dead flesh, has no intestines and no bladder anymore, is being punished	Suspect or likely	Absent	Definite
10/63/m	Has no money anymore, is bankrupt, ruined his family, is worthless, thus is not allowed to eat, to drink or to urinate	Definite	Absent	Absent

Table 2 continues

Table 2 (continued) Delusional symptoms of psychotic patients (n = 15)

Case#/ Age/Sex	Delusional symptoms as actually reported by the patient	Delusions according to SADS score		
		Guilt/Sin	Persecutory	Somatic
12/45/m	The police is after him; has big financial debts, the admission is a punishment for all of his crimes; cannot pay food	Definite	Absent	Suspect or likely
13/44/f	Makes everybody ill, is a devil, is guilty of everything, is already dead; family hates her and will punish her	Definite	Absent	Suspect or likely
14/46/m	Is a criminal, has killed his wife, evaded taxes, the hospital is a prison, his house is burned down as a punishment	Definite	Definite	Absent
15/52/f	Deserves to go to prison, did everything wrong, has deceived everybody; everybody thinks she is crazy and evil	Definite	Absent	Absent

significance. Each patient given a diagnosis of psychotic depression was shown to manifest at least one mood-congruent delusional belief as defined by the SADS. The delusions in the psychotic patients consisted of delusions of guilt or sin, persecutory delusions or somatic delusions (Table 2). One of the non-psychotic subjects who did not respond to treatment had a diagnosis of a bipolar disorder. Six patients dropped out and 1 patient was excluded from analyses because blood levels revealed poor compliance (Table 3). Thus, 45 subjects were able to complete the study, of which 13 were diagnosed with psychotic depression. Seven patients, 5 non-psychotic and 2 psychotic, were treated with valerian extract. Three patients were treated with concomitant psychotropic medication; 1 non-psychotic patient with lorazepam, 1 psychotic patient with haloperidol and 1 psychotic patient with lorazepam and haloperidol. All 3 did not respond to treatment: thus, neither haloperidol nor lorazapam could have been instrumental in the recovery of patients. No other sedatives, hypnotics or other psychotropics were used by any of the patients.

Table 3. Dropouts and completers by non-compliance ($n = 7$)

	Reason	
Psychotic	Deterioration	1
	Fever and delirium	1
Non-psychotic	Mania	1
	Orthostasis	1
	Allergic reaction	2
	Non-compliance (blood level ↓)	1

Treatment periods, blood levels and doses

Predefined blood levels of imipramine were achieved after 12.8 days (mean SD ± 5.2, range 7-25) for the psychotic patients, and after 14.0 days (mean SD ± 4.4, range 7-24) for the non-psychotic patients. Thus, the mean total period of imipramine treatment (including 4 weeks of treatment at predefined blood levels) was 40.8 days (SD ± 5.2, range 35-53) for the psychotic patients, and 42 days (SD ± 4.4, range 35-52) for the non-psychotic patients (i.e. a mean of almost 6 weeks for both groups).

The mean daily dose after attaining the predefined blood level for the psychotic patients was 211 mg (SD ± 103.5, range 37.5-337.5) with a mean blood level of 270 μg/l (SD ± 31.5, range 213.5-320.3; sum of imipramine and desmethyl-imipramine). The mean daily dose for the non-psychotic patients was 247 mg (SD ± 85.5, range 112.5-450) with a mean blood level of 265 μg/l (SD ± 38.3, range 199.0-400.3).

Treatment effects

Nine of the 13 (69.2%) psychotic patients and 14 of the 32 (43.8%) non-psychotic patients responded to treatment according to the 50% response criterion ($\chi^2 = 1.5$; $df = 1$; p = n.s.). (95%-confidence interval comparing the psychotic group and non-psychotic group of subjects -4.9%; +55.9%).

Eight of the 13 (61.5%) psychotic patients and 9 of the 32 (28%) non-psychotic patients were reported as "in remission" (HRSD <10; Fisher's Exact Test: $p = 0.048$) (95% confidence interval: 2.8%; 64.2%).

Multiple regression analysis controlling for potential confounding factors showed a significant lower mean outcome HRSD score in the psychotic group compared to the non-psychotic group of patients (-6.6; SE B = 2.91; 95% CI (-12.5; -0.70); t = -2.27; $df = 37$; $p = 0.03$) (Table 4). Furthermore, the relationship between mean outcome HRSD score and the duration of the present episode of illness was also shown to be statistically significant. Subjects whose current episode of illness had a duration of less than or equal to 1 year were found to have a significantly lower mean outcome HRSD score (6.79; SE B = 2.78; 95% CI (1.16; 12.42); $t = 2.44$; $df = 37$; $p = 0.02$).

Figure 2 shows the mean MADRS scores of all completers for the 2 groups during 6 weeks of treatment. According to the rm-ANOVA there was a difference in change in MADRS scores over time between psychotic and non-psychotic patients controlled for confounding factors ($p = 0.011$), which indicated a statistically significant steeper decline in MADRS scores for the group of patients diagnosed with psychotic depression. In the psychotic patients, the trend was found to be 1.75 (SE = 0.680) MADRS units per week lower than in the non-psychotic patients, adjusted for the earlier mentioned co-variables. The difference in mean MADRS scores at baseline between psychotic and non-psychotic subjects who completed this study was not significant ($p = 0.22$).

Table 4. Results of a multiple regression analysis concerning the effect of psychotic features and possibly confounding variables in the HRSD-outcome score. The regression coefficient (B) indicates the increase (B: +) or decrease (B: -) of the HRSD outcome score for each unit increase in the variable

Variable (units)	B (SE)	95% CI	*p*
Psychotic features (no = 0, yes = 1)	-6.60 (2.91)	-12.50; - 0.70	0.03
Age (years)	0.01 (0.13)	- 0.25; 0.28	0.92
Duration of present episode ($\leq$ 1 year =0, >1 year =1)	6.79 (2.78)	1.16; 12.42	0.02
Number of previous depressions	1.96 (2.74)	- 3.60 ; 7.52	0.48
Family history (no = 0, yes = 1)	3.36 (2.68)	- 2.06 ; 8.79	0.22
Baseline severity (HRSD score)	0.35 (0.29)	- 0.24 ; 0.93	0.24
Retarded depression (RDC) (no = 0, yes = 1)	5.28 (3.08)	- 0.97 ; 11.53	0.10

Discussion

In this study a high response rate of approximately 70% was observed in our patients with psychotic depression who were treated with imipramine with no adjuvant antipsychotic medication. This contrasted with a much lower response rate of about 40% to the same treatment in our non-psychotic patients. Throughout the entire treatment period the steeper response curve of the psychotic depressed patients in the present study was clear (Figure 2). Possible confounding factors did not account for this result. On the contrary, the difference in response between psychotic and non-psychotic groups of patients was more pronounced after potential confounding factors had been controlled for. The only co-variable that was shown to contribute significantly to the difference in treatment response observed between psychotic and non-psychotic patients, was "duration of the present episode", i.e. a longer duration of the present episode was related to a poorer treatment response in line with the literature (Scott, 1994). The fact that our patients with psychotic depression had a shorter duration of the present episode (Table 1A) and a better treatment response (Table 4) might suggest that "duration of the episode" and not psychosis status explains our observed differences in treatment response. This, however, is refuted by the fact that the effect of psychosis status in the mean HRSD outcome was even more significant in the analysis adjusting for "duration of the present episode" as a confounder (Table 4).

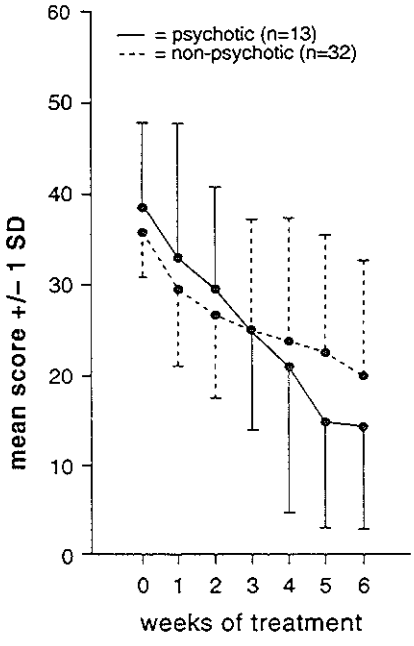

Figure 2 Mean total score on the Montgomery-Åsberg Depression Rating Scale of all subjects who completed the study. Difference in time-trend: $p = 0.011$

The fact that the present results form part of a randomised double-blind trial comparing imipramine with mirtazapine helps clarify another alternative explanation of the results. Imipramine was shown to be significantly superior to mirtazapine in the treatment of our psychotic as well as non-psychotic patients (Bruijn et al., 1996); this rules out possible explanation of our results being related to high placebo response in both or either of the comparison groups.

Most studies report a low response rate (23-40%) for patients with psychotic depression when treated with tricyclic antidepressants alone (Schatzberg and Rothschild, 1992; Chan et al., 1987). The difference in response rate observed in the present study could be accounted for by variations in methodology. Optimal dosing in our study may explain our high treatment response rates. Earlier studies frequently did not provide a clear report of dosage and duration of the drug treatment and most did not control for blood levels of the studied tricyclic antidepressant. Considering the extreme range of doses (37.5-450 mg) which we

found to be necessary to adjust the dose to the predefined, adequate, blood level of imipramine in this study, an other way of dosing could not have resulted in treatment with adequate blood levels of imipramine in all patients. This raises the possibility of sub-optimal dosing of antidepressants in other studies. Since psychotic depressed patients may show a lower placebo response than non-psychotic depressed patients (Schatzberg and Rothschild, 1992), sub-optimal dosing could reduce the response in psychotic patients more than in non-psychotic patients. There are, however, other studies of psychotic depressed patients using measurement of blood antidepressant levels, which report a lower treatment response rate for psychotic depressed patients. Glassman et al. (1975) found a considerable and significant response difference between psychotic and non-psychotic depressed patients treated with imipramine. Patients were treated during 4 weeks with a fixed dose of 3.5 mg of imipramine per kg body weight (average daily dose for men 250 mg, for women 200 mg). The blood levels obtained with this treatment regimen, however, were not reported. In a report on the possible clinical implications of plasma imipramine levels for the management of depressive illness, Glassman et al. (1975) could not detect a relationship between therapeutic response and antidepressant blood level in the psychotic patients in contrast to his findings for the non-psychotic group of patients. However, of the 17 psychotic patients in this study, only 9 patients had an imipramine plus desipramine blood level in excess of 180 ng/ml.

Quitkin et al. (1978) have reported a satisfactory treatment response by patients with psychotic depression to tricyclic medication alone (i.e. not combined with an antipsychotic preparation), and argued that other authors found a difference in favour of non-psychotic depressed patients, because the duration of their treatment period was only 4 weeks. This argument is not supported by our results, however, because the therapeutic response in the present study after a mean of ca. 4 weeks of treatment was not found to be worse for psychotic patients than for non-psychotic patients (Figure 2).

The results of the double-blind blood level controlled study of Spiker et al. (1985), in which patients were randomly assigned to amitriptyline alone, to perphenazine alone or to amitriptyline plus perphenazine, are also not in line with our results. Spiker et al. did report the mean blood level of antidepressant during the 35 days of treatment, but they did not report how many days the patients were treated on an adequate blood level of amitriptyline plus nortriptyline (Spiker et al., 1985; Spiker et al., 1986). Also, in this study the patient group with combination

treatment had a higher mean blood level of the antidepressant than the patient group treated with the antidepressant alone. Nevertheless, it is not clear whether this could explain the difference in results.

Comparison of results also raises the question whether the patients selected in different studies are comparable. In this regard the classification of psychotic and non-psychotic patients is important. In the present study all psychotic patients have mood-congruent delusions as is also the case in the study by Glassman et al. (1975). In other studies the qualification "mood-congruence" in terms of delusions is not explicitly mentioned. Thus, it is not clear whether the patients are comparable to our subjects with respect to this characteristic. Depressed patients with delusions, which are not mood-congruent, may be less likely to respond to treatment with antidepressants alone compared to combination therapy of antidepressant and antipsychotic medication (May et al., 1990; Parker et al., 1992).

Another possible difference between patient populations in different studies, may be the mean age of patients recruited: in Glassmans' study the mean age of subjects was about 10 years higher than in our study.

A further difference may be the almost complete lack of concomitant medication in our study, which is in contrast to other studies. It is conceivable that other medications - such as anxiolytic preparations – improve treatment response in non-psychotic, but not in psychotic depressed patients (Schatzberg and Rothschild, 1992).

Glassman et al. (1975) made reference to the issue of severity as a confounding factor in the comparison of the response rates of psychotic depressed and non-psychotic depressed patients. Kocsis et al. (1990) reported that the treatment response of severely depressed patients with no psychotic features did not differ significantly from the response of those with psychotic depression and that both groups fared worse than the group of moderately depressed patients with no psychotic features. Kocsis suggested the difference in response noted between the groups was more being related to severity of illness than to the psychotic / non-psychotic dichotomy. In the present study this is not the case, because our group of non-psychotic patients showed a lesser treatment response compared to the more severe group of psychotic patients (Tables 1A, 1B).

The fact that only 15 of the 52 patients recruited into this study were psychotic may caution against generalisation of the results. However, there are no well-controlled studies with substantially larger numbers of psychotic depressed patients. In no way, however, does this restricted number explain away the high response rate

to imipramine mono-therapy that we observed in our group of patients with psychotic depression.

Most reports in the literature conclude that combination of an antidepressant with a neuroleptic drug is the treatment of choice in psychotic depressed patients in view of the poor response to mono-therapy with an antidepressant. In our patient group, however, the first choice treatment is mono-therapy with imipramine with blood level control because of the high success rate, the more so since subsequent lithium addition for psychotic depressed patients with unsatisfactory response increased the response rate from 69% to 100% (Bruijn et al., 1998).

Our belief is that our findings need to be tested further in a prospective study and further double-blind, randomised controlled studies, comparing combination therapy with antidepressant mono-therapy in psychotic depressed patients similar to our study population, are also warranted to clarify the issues discussed in this paper.

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4 | Depressed inpatients respond differently to imipramine and mirtazapine

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Chapter 4

Depressed inpatients respond differently to imipramine and mirtazapine

Abstract

Tricyclic antidepressants and more recent antidepressants are generally considered to have equivalent efficacy in the treatment of depression. After a previous report of a marked difference in the response to mirtazapine compared to imipramine, we report here an analysis of different symptom clusters. One hundred and seven consecutive inpatients with major depression (Diagnostic and Statistical Manual III-R, DSM-III-R) and a Hamilton Rating Scale for Depression (HRSD) score of 18 points or more were randomly assigned to double-blind treatment. Two and 4 weeks after predefined blood levels had been obtained, the severity of depression was assessed using the HRSD. The mean dosages used were 235 mg/day of imipramine and 77 mg/day of mirtazapine, the latter being in excess of the 15-45 mg/day range currently advised. Total HRSD scores and 7 symptom clusters were analysed in the 85 patients (79%) who were not receiving any co-medication. Imipramine was more effective against the clusters related to core symptoms of depression: "depression and guilt", "retardation" and "melancholia", respectively. Mirtazapine showed a biphasic response with regard to the clusters "sleep" and "anxiety/agitation", respectively, which consisted of a marked response after 2 weeks of predefined blood level, but with a waning of this effect at 4 weeks. Imipramine produced a more gradual response on these clusters, which was more pronounced at 4 weeks than with mirtazapine. Two aspects of the present study could be related to this finding: blood level control resulted in optimal treatment with imipramine but not mirtazapine and - most importantly – the patients were not receiving any anxiolytic or hypnotic co-medication. These findings suggest that mirtazapine may have anxiolytic and sedative properties and fewer antidepressant properties than imipramine in severely depressed inpatients.

Introduction

It is generally considered that different antidepressants have similar efficacy (Burke and Preskorn, 1995; Song et al., 1993). Efforts to identify patient

characteristics capable of predicting the response to a specific serotonin re-uptake inhibitor (SSRI), for example - compared with mixed re-uptake inhibitors such as tricyclic antidepressants - have been unsuccessful (Burke and Preskorn, 1995). The same applies to efforts to identify specific symptoms responsive to a single antidepressant (Danish University Antidepressant Group, 1986; 1990; 1993).

In a previous report on this study, we described a significant difference in response in favour of imipramine in a double-blind, fixed blood level study comparing imipramine with mirtazapine in depressed inpatients (Bruijn et al., 1996). Mirtazapine is a new antidepressant related to mianserin and pharmacologically different from the tricyclic antidepressant imipramine. It is a strong antagonist of central α_2 adrenoreceptors, serotonin $5HT_2$ and $5HT_3$ receptors, and histamine H_1 receptors and a weaker antagonist of muscarine and α_1 adrenoreceptors (De Boer et al., 1995). Imipramine is a strong mixed (norepinephrine, serotonin) re-uptake inhibitor with strong anticholinergic properties and weaker antagonism of H_1 and α_1 receptors. In a more detailed analysis of the course of the Hamilton Rating Scale for Depression (HRSD) total scores (Hamilton, 1960) and of symptom clusters over time during treatment, we detected differences in patterns of response between the 2 drugs, which might be indicative of differences in the drugs' mechanism of action.

Patients and methods

General outline (Figure 1) and patient population

Patients included were aged 18-65 with a Diagnostic and Statistical Manual III-R (DSM-III-R) diagnosis of "major depressive episode", which was assessed by 2 psychiatrists on the basis of the depression section of the Schedule for Affective Disorders and Schizophrenia (SADS; Spitzer and Endicott, 1978/79) and with a HRSD score of 18 or more. Patients with hallucinations, schizophrenia, paranoid psychosis, organic brain syndrome, chronic drug or alcohol abuse, and clinically relevant somatic diseases were excluded.

After written informed consent had been received, a single-blind placebo was administered for 4 days. On the 5th day, patients were assessed again on the HRSD, and those still meeting the inclusion criterion of an HRSD score of 18 or more were randomly allocated to double-blind treatment with either imipramine or mirtazapine. Blood levels were monitored weekly, and dosages of both drugs were adjusted (by an independent psychiatrist, to preserve blindness) to obtain fixed blood levels (200-300 μg/l for imipramine + desmethyl-imipramine (Perry et al., 1987) and 50-100 μg/l for mirtazapine). The blood level of mirtazapine was based on a pilot study with 20

patients receiving 60 mg/day of mirtazapine (Bruijn et al., 1996). The HRSD was assessed 2 and 4 weeks after this blood level was reached. No psychotropic medication apart from the study medication was allowed except for 1 to 6 tablets a day each containing 45 mg of an extract of valerian, in case of anxiety or insomnia. This extract was presumed to be without antidepressant effect.

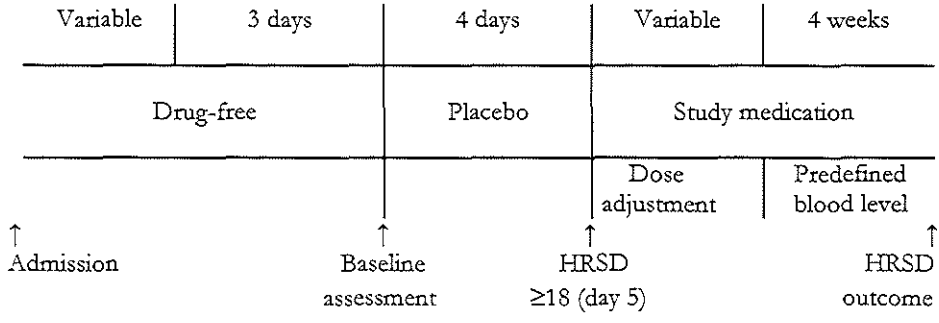

Figure 1. General outline of the study design

One hundred seven depressed inpatients were randomly assigned to active treatment. Eight patients dropped out, and 2 patients were excluded from analyses because blood levels showed non-compliance (Table 1); 97 patients (51 taking mirtazapine and 46 taking imipramine) completed the study. All patients were drug-free when they started on the study medication. Nine mirtazapine and 7 imipramine patients were treated with valerian extract. There were no significant differences between the 2 treatment groups with respect to the dose and duration of valerian medication. The protocol allowed for co-medication only in case of intolerable agitation or anxiety, and/or intolerable psychotic symptoms. Nine of the 51 patients taking mirtazapine (18%) and 3 of the 46 patients taking imipramine (7%) were treated with lorazepam 1-5 mg/day and/or haloperidol 1-15 mg/day (Table 1), respectively, for these reasons.

As this report is concerned with differences in the patterns of response to the 2 antidepressants investigated, it describes the results of the group of 85 completers (79%) who had no concomitant medication (Table 2). Predefined blood levels in the 42 mirtazapine patients were achieved after 11.3 days (mean SD ± 3.5, range 5-21), and for the 43 imipramine patients after 13.5 days (mean SD ± 4.5, range 7-25), respectively. Thus, the mean total period on study medication (including 4 weeks on

predefined blood levels) was 39.3 days (SD ± 3.5, range 33-49) for mirtazapine and 41.5 days (SD ± 4.5, range 35-53) for imipramine, i.e. almost 6 weeks. The daily dose after the predefined blood level for mirtazapine was reached, was 77.4 mg (mean SD ± 17.6, range 40-100) with a blood level of 69.0 µg/l (mean SD ± 8.8, range 52.3-89.0), and for imipramine 235.5 mg (mean SD ± 90.8, range 37.5-450) with a blood level of 267.6 µg/l (mean SD ± 36.5, range 195.0-400.3; sum of imipramine and desmethyl-imipramine), respectively.

Table 1. Drop-outs, non-completers by non-compliance, and protocol violation by concomitant medication (n = 22)

Reason	Mirtazapine (n = 12)		Imipramine (n = 10)	
Drop-out/non-compliance	Transfer to other ward	1	Mania	1
	Refusal to take medication	1	Orthostasis	1
	Non-compliance (blood level ↓)	1	Deterioration	1
			Fever and delirium	1
			Allergic reaction	2
			Non-compliance (blood level ↓)	1
Concomitant medication	Lorazepam	2	Lorazepam	1
	Haloperidol	5	Haloperidol	1
	Lorazepam + haloperidol	2	Lorazepam + haloperidol	1

Data analysis and statistical methods

During the pre-planned statistical analysis of this study, reported elsewhere (Bruijn et al., 1996), we observed differences in the time course of the HRSD total scores during treatment (Figure 2). These differences between mirtazapine and imipramine were analysed using repeated measures-ANOVA for unbalanced data (BMDP software program). The following HRSD symptom clusters were analysed in the same way: "depression + guilt" (items 1 + 2 + 3), "sleep disturbances" (items 4 + 5 + 6), "retardation" (items 7 + 8), "anxiety/agitation" (items 9 + 10 + 11), "somatic complaints" (items 12 + 13), and "others" (items 14 + 15 + 16 + 17) (Danish University Antidepressant Group, 1986; 1990; 1993), along with the HRSD factor "melancholia" (items 1 + 2 + 7 + 8 + 10 + 13) (Bech et al., 1975).

Table 2. Characteristics of the patient population (n = 85)

	Mirtazapine (n = 42)	Imipramine (n = 43)
Age: mean ± SD (range)	44 ± 10 (26 - 65)	49 ± 10 (29 – 65)
Sex: male/female	9/33	8/35
Diagnosis (DSM-III-R) "major depressive episode"	42	43
* *Unipolar*	38	42
Non-psychotic, 1st episode	18	19
Non-psychotic, recurrent	13	12
Psychotic, 1st episode	4	7
Psychotic, recurrent	3	4
* *Bipolar* Non-psychotic	4	1
Melancholic type	36	38
Major Depressive episode (RDC)	42	42
Retarded Depression (RDC)	31	31
Agitated Depression (RDC)	30	28
Endogenous Depression (RDC)	41	40
Suicidal (RDC)	22	25
HRSD-baseline ± SD (range)	25.3 ± 4.1(19 - 37)	26.3 ± 4.8(18 – 37)
MADRS-baseline ± SD (range)	36.1 ± 5.5(25 - 48)	36.3 ± 5.8(27 – 54)
Duration current episode		
< 1 year	25	27
> 1 year	17	16
Adequate pre-treatment with antidepressants	25	19
Family history (1st/2nd degree)		
Depression	22	23
Suicide	7	7

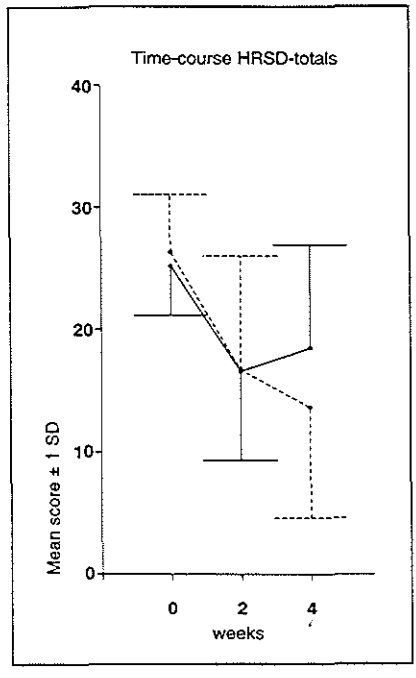

Figure 2 Mean total scores on the 17 item-HRSD ± 1 SD (vertical axis) of the 42 mirtazapine completers and 43 imipramine completers without co-medication, at baseline and 2 and 4 weeks after attaining the predefined blood level of the study medication (horizontal axis). Solid line = mirtazapine; dotted line = imipramine. The time course is significantly different between mirtazapine and imipramine according to repeated measures ANOVA ($p < 0.005$).

There were 3 repeated measurements of these dependent variables: 1 at baseline (measurement 0) and 2 measurements during the trial - measurement 1 after 2 weeks and measurement 2 after 4 weeks of the predefined blood level of the antidepressant. The between-subject factor was treatment with 2 levels: "mirtazapine" and "imipramine". Firstly, a restricted model was fitted, only including a categorical within-subject time factor, with the following coefficients: β_0 for the baseline level, β_1 for the difference from baseline at measurement 1, and β_2 for the difference from baseline at measurement 2. Secondly, the restricted model was extended to a full model by adding interactions between the within-subject time factor and the dichotomous between-subjects treatment factor, thus allowing the coefficient β_1 and β_2 to be different between the 2 treatment groups. Because the treatment factor is

randomised, the baseline coefficient β_0 is by definition the same in both treatment groups. The effect of treatment was tested by comparing the full model with the restricted model, using a likelihood ratio test with 2 degrees of freedom. The 3 x 3 within-subject co-variance matrix of the residuals was left completely unstructured. The likelihood ratio test thus assessed whether the 2 coefficients β_1 and β_2 were different simultaneously between the 2 treatment groups; hence, the difference in the time-course between the 2 treatment groups during treatment was tested. As a co-variate, the time from baseline to reach the predefined blood level of mirtazapine or imipramine was included in all the models considered, which adjusted the results for between-subject difference in this time.

Ethical considerations

The protocol was approved by the Ethics Committees of the University Hospital "Dijkzigt" and of the Medical Faculty of the University of Rotterdam.

Results

The scores on all symptom clusters appeared to decrease steadily between baseline and 2 and 4 weeks of predefined blood level for imipramine, while for mirtazapine 2 different patterns appeared. On the one hand (Figure 3), the scores for the symptom clusters "depression and guilt", "retardation" and "melancholia" decreased less for mirtazapine than for imipramine at both time points. On the other hand (Figure 4), the scores for the symptom clusters "sleep disturbances" and "anxiety/agitation" decreased more for mirtazapine than for imipramine up to 2 weeks of predefined blood levels, while these scores increased again between 2 and 4 weeks of predefined blood levels, in contrast to the scores for imipramine.

Table 3 shows the mean and 95% confidence intervals for the difference between the HRSD total scores and the symptom clusters between the 2 treatment groups at measurement 1 and measurement 2, respectively, estimated by the model. The time course of the HRSD total scores was significantly different between the 2 drug groups according to the repeated-measures ANOVA ($\chi^2 = 11.0$, degrees of freedom (df) = 2, $p < 0.005$, Figure 2). The time course of most HRSD symptom clusters analysed was also significantly different between imipramine and mirtazapine; "depression and guilt" χ_2=8.44, df=2, $p < 0.025$, "retardation" $\chi_2 = 14.48$, $df = 2$, $p < 0.001$, "melancholia" $\chi_2 = 6.43$, $df = 2$, $p < 0.05$, "sleep disturbances" $\chi_2 = 9.36$, $df = 2$, $p < 0.01$, "anxiety/agitation" $\chi_2 = 7.09$, $df = 2$, $p < 0.05$. However, there was no

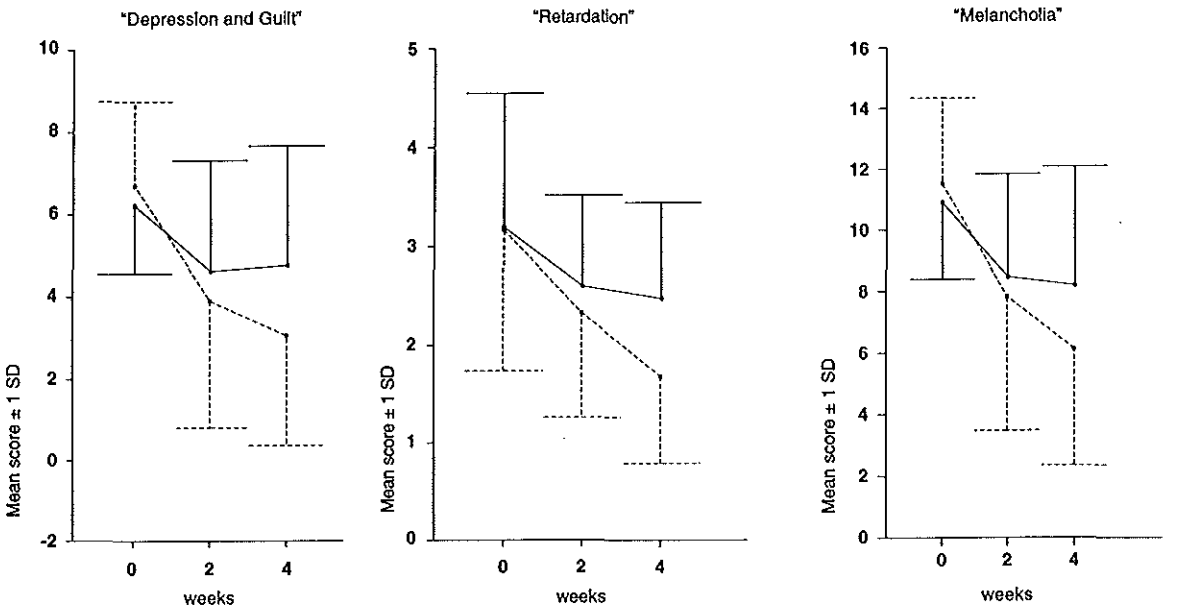

Figure 3 Mean total scores ± 1 SD of the the HRSD symptom clusters "depression and guilt" (items 1 + 2 + 3), "retardation" (item 7 + 8) and "melancholia" according to Bech et al. (1975) (items 1 + 2 + 7 + 8 + 10 + 13), (vertical axis); and of the 42 mirtazapine completers and 43 imipramine completers without co-medication, at baseline and 2 and 4 weeks after attaining the predefined blood level of the study medication (horizontal axis). Solid line = mirtazapine, dotted line = imipramine. The time courses for these 3 symptom clusters are significantly different between mirtazapine and imipramine according to rm ANOVA ($p < 0.025$, $p < 0.001$, and $p < 0.05$, respectively).

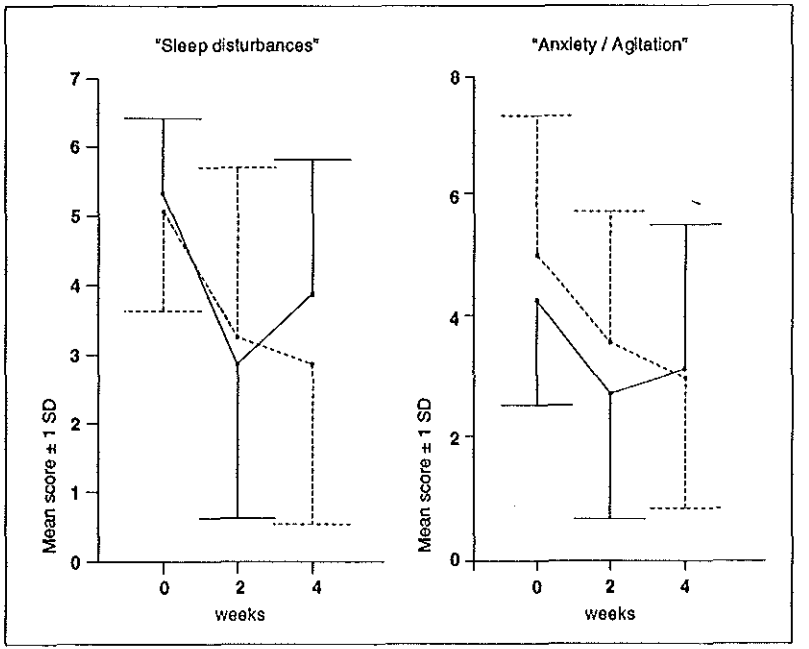

Figure 4 Mean total scores of the HRSD symptom clusters "sleep disturbances" (items 4 + 5 + 6) and "anxiety/agitation" (items 9 + 10 + 11), (vertical axis) for the 42 mirtazapine completers and 43 imipramine completers without co-medication, at baseline and 2 and 4 weeks after attaining the predefined blood level of the study medication (horizontal axis). Solid line = mirtazapine and dotted line = imipramine. The time courses for these 2 symptom clusters are significantly different between mirtazapine and imipramine according to rm ANOVA ($p < 0.01$ and $p < 0.05$, respectively).

significant difference for the symptom clusters "somatic complaints" $\chi_2 = 0.97$, $df = 2$, p: n.s.; and "others" $\chi_2 = 6.02$, $df = 2$, p: n.s.

To avoid the pitfall of these results being artefacts of selecting only the patients completing the study without taking any co-medication, we carried out the same analyses with the group of all 107 patients (intent to treat, with last observation carried forward) also including dropouts and patients with co-medication, and with the group of all 97 completers excluding dropouts, but including all patients with co-medication. The results of these analyses were similar to the results of the group of 85 completers without any co-medication.

Table 3. Mean (D) and 95% confidence intervals (95% CI) of the difference between the 2 treatment groups at measurement 1 and measurement 2, respectively, estimated by the model. HRSD total scores and symptom clusters (negative values indicate superiority of imipramine).

	Measurement 1		Measurement 2	
	D	95% CI	D	95% CI
HRSD total scores	-0.2	- 3.6/+3.3	- 4.8	- 8.5/- 1.1
Depression and guilt	-0.8	- 2.0/+0.4	- 1.8	- 2.9/- 0.6
Retardation	-0.2	- 0.6/+0.2	- 0.7	- 1.1/- 0.4
Melancholia	-0.8	- 2.4/+0.8	- 2.0	- 3.6/- 0.4
Sleep disturbances	+0.6	- 0.4/+1.5	- 0.9	- 1.7/- 0.0
Anxiety/agitation	+0.5	- 0.3/+1.4	- 0.4	- 1.3/+0.5
Somatic complaints	-0.2	- 0.7/+0.3	- 0.3	- 0.8/+0.3
Other symptoms	+0.3	- 0.4/+1.0	- 0.5	- 1.3/+0.3

Discussion

Differences in response patterns between imipramine and mirtazapine were identified in depressed inpatients. Imipramine was more effective for symptoms such as depression, guilt, and retardation, which can be regarded as the core symptoms of depression (Bech et al., 1975) and it had an effect on all of the symptoms, which progressively increased during treatment. Mirtazapine, on the other hand, had a more restricted effect on sleep and anxiety symptoms, to which tolerance developed.

Differences in the response patterns have not previously been observed in studies comparing antidepressants, despite the wealth of such studies and numerous efforts to discover differences between antidepressants (Burke and Preskorn, 1995; Danish University Antidepressant Group, 1986; 1990; 1993; Song et al., 1993). We believe that two aspects of this study contributed to the differences found.

First, the problem of correct dosing of imipramine was solved by adjusting the dose to obtain a fixed blood level. Other studies did not apply this methodology, and used either gradual titration or aggressive dosing. It has been pointed out that the former frequently results in inadequate antidepressant doses, in contrast to the latter, which results in large dropout rates (Burke and Preskorn, 1995). Thus, the present study appears to stand out from other studies in that it adjusted adequate dosage of imipramine in all patients, together with a low dropout rate. With mirtazapine, it was not possible to predefine an optimal blood level, because therapeutic blood levels of mirtazapine are not available. The predefined blood level of mirtazapine was based on steady-state blood levels of 20 patients receiving 60 mg/day of mirtazapine (Bruijn et al., 1996). This dosage was advised by Organon for the treatment of depressed patients at the time when the study started. By adjusting mirtazapine doses to this predefined blood level, we excluded treatment under extremely high or low blood levels, and ascertained treatment compliance. The mean mirtazapine dose of 77 mg/day was above the dosages used in other inpatient studies - 47 mg/day (Richou et al., 1995) and 53 mg/day (Zivkov and De Jong, 1995), respectively. The dose currently advised by Organon is 15-45 mg/day. No dose-response studies with mirtazapine are available that show reduced effectiveness at higher dosages, but it cannot be ruled out that this higher dosage influenced our results.

Secondly, the 85 patients described here did not receive any concomitant anxiolytic, hypnotic, or sedative medication, except for the few who were treated with the supposedly inactive valerian extract. It has been suggested that a co-medication with benzodiazepines may mask differences in efficacy between antidepressants (Angst, 1993), and this certainly would apply to differences in symptom clusters involving sleep and anxiety.

Tricyclic antidepressants such as imipramine may be more effective in severely depressed inpatients (Burke and Preskorn, 1995; Danish University Antidepressant Group, 1986; 1990; 1993) such as our patient population, in which 47 patients were suicidal and 18 patients were psychotic in the total of 85. Typical patients included in clinical trials during drug development form a heterogeneous group of outpatients suffering from mild to moderate depression without suicidal or psychotic features (Burke and Preskorn, 1995). It would seem prudent not to generalise the present

findings to populations of depressed patients. The analyses of response patterns were carried out post hoc, and require replication. If replicated, the results would imply that mirtazapine has sedative and anxiolytic properties, and fewer antidepressant properties than imipramine. This must be related to the different pharmacological properties of the drugs. Mirtazapine is a strong antihistaminic, in contrast to imipramine (Richelson, 1982). Histamine antagonists are sometimes prescribed for the treatment of anxiety (Rickels and Schweizer, 1987), they shorten sleep latency (Roehrs et al., 1993), and histamine has been implicated in the control of the waking state (Monti, 1993). Mirtazapine has been shown to have hypnotic properties (Ruigt et al., 1990). Development of tolerance to the effects of histamine antagonists has been described (Tinklenberg, 1977). Mirtazapine is also a strong antagonist of serotonin-2/1C receptors (De Boer et al., 1995), in contrast to imipramine (Richelson, 1982). Antagonism of these receptors has been associated with anxiolytic effects in patients with dysthymia or generalised anxiety disorder (Blackburn 1992). Imipramine is a potent inhibitor of serotonin and norepinephrine re-uptake (Rickels and Schweizer, 1987), in contrast to mirtazapine (De Boer et al., 1995). Whether one or more of these properties can explain the differences observed remains to be investigated.

Imipramine, mirtazapine, SSRIs and other antidepressants in one way or another stimulate serotonergic neurotransmission via $5HT_{1A}$ receptors in the hippocampus (Blier and DeMontigny, 1994; Haddjeri et al., 1996). This is assumed to be related to the clinical antidepressant effects (Blier and DeMontigny, 1994; Haddjeri et al., 1996). The results of the present study point to a difference between imipramine and mirtazapine, specifically with regard to antidepressant properties. This argues against the view that their common stimulation of serotonergic neurotransmission was related to the clinical antidepressant effects observed in our patients.

The findings of this study my have implications for the way in which clinical trials with antidepressants should be carried out and the theories about which properties are related to the antidepressant effects of drugs. Before we reach that point, however, similar results must be obtained elsewhere and with other antidepressants in trials using fixed blood levels and without concomitant medications.

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5 | Comparison of 2 treatment strategies for depressed inpatients: Imipramine and lithium addition or mirtazapine and lithium addition

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Chapter 5

Comparison of two treatment strategies for depressed inpatients: Imipramine and lithium addition or mirtazapine and lithium addition.

Abstract

Background: The purpose of this study was to compare the overall effectiveness of two treatment strategies for inpatients with severe major depressive episode (DSM-III-R: (1) Mirtazapine (phase 1) and subsequent lithium addition (phase 2) or (2) imipramine (phase 1) and subsequent lithium addition (phase 2). We previously reported the results of phase 1.

Method: In phase 1, patients were randomly assigned to treatment with either mirtazapine or imipramine, and doses were adjusted to obtain predefined blood drug levels. Non-responders had lithium added to the double-blind mirtazapine or imipramine medication. The dose was adjusted to obtain a blood level of 0.5 to 1.0 mmol/l. Treatment effects were evaluated weekly by the Montgomery-Åsberg Depression Rating Scale for up to 2 weeks on this lithium blood level.

Results: Data for 100 patients were available for comparison of the 2 treatment strategies. Eighty patients received no co-medication. By the end of phase 2, 24 (48%) of 50 had responded to mirtazapine and 32 (64%) of 50 had responded to imipramine (intent-to-treat analysis). A survival analysis of the total patient group intent-to-treat showed a significant difference in favour of the treatment strategy with imipramine and subsequent lithium addition.

Conclusion: Efficacy of imipramine and subsequent lithium addition for non-responders is superior to the same treatment strategy with mirtazapine. This applies to the patient sample studied, which consisted of 100 severely depressed inpatients, 29 of whom were psychotically depressed. More serious side effects of imipramine, however, led to discontinuation of imipramine in 5 patients. No serious side effects were observed during the phase of lithium addition to either imipramine or mirtazapine. We, therefore, prefer to start treatment with imipramine and test for fixed blood drug levels, and, if necessary, add lithium. In the case of prohibitive side effects, patients are switched to a modern antidepressant such as mirtazapine and, if necessary, lithium is added to this antidepressant.

Keywords

Mirtazapine; Imipramine; Lithium addition; Treatment strategy; Major Depression.

Introduction

Many clinical reports and open studies and a few double-blind studies suggest lithium addition to be an effective strategy for treatment resistant depression in about 50% to 60% of cases (Schöpf, 1989a). Although most double-blind studies deal with small numbers of patients (De Montigny et al., 1983; Heninger et al., 1983; Kantor et al., 1986; Katona et al., 1995; Schöpf et al., 1989b; Stein and Bernadt, 1988; Zusky et al., 1988) 2 meta-analyses of these studies confirm the effectiveness of lithium addition (Austin et al., 1991; Katona et al., 1995).

As a result, it is quite common in clinical practice to add lithium to an antidepressant in the case of non-response to the latter. The treatment with an antidepressant and the addition of lithium to it, however, are seen as separate, unrelated treatment decisions; e.g., in prescribing an antidepressant, clinicians do not take into account the efficacy of a possible lithium addition with that particular antidepressant, although results of lithium addition may differ between antidepressants. Similarly, in studies of lithium addition, non-responders to an antidepressant are mostly recruited without much attention for details of the treatment phase that resulted in non-response (Schöpf, 1989a; Katona, 1995).

In the present study, lithium was added to the treatment of inpatients that were treatment-resistant in a randomised, double-blind, fixed blood level study comparing mirtazapine with imipramine. Mirtazapine is a new antidepressant of the group of the piperazinoazepines, related to mianserin. It is a strong antagonist of central α_2-adrenoreceptors, serotonin $5HT_2$ and $5HT_3$ receptors, and histamine H_1 receptors and is a weaker antagonist of muscarine and α_1 adrenoreceptors (De Boer et al., 1995). The results of the comparative trial, before lithium addition, indicated a large, statistically significant and clinically relevant difference in efficacy in favour of imipramine (Bruijn et al., 1996).

The purpose of the present study was to compare the overall response of a two-step treatment strategy with a standard tricyclic antidepressant and lithium addition for non-responders with a similar treatment strategy with mirtazapine and subsequent lithium addition.

Methods

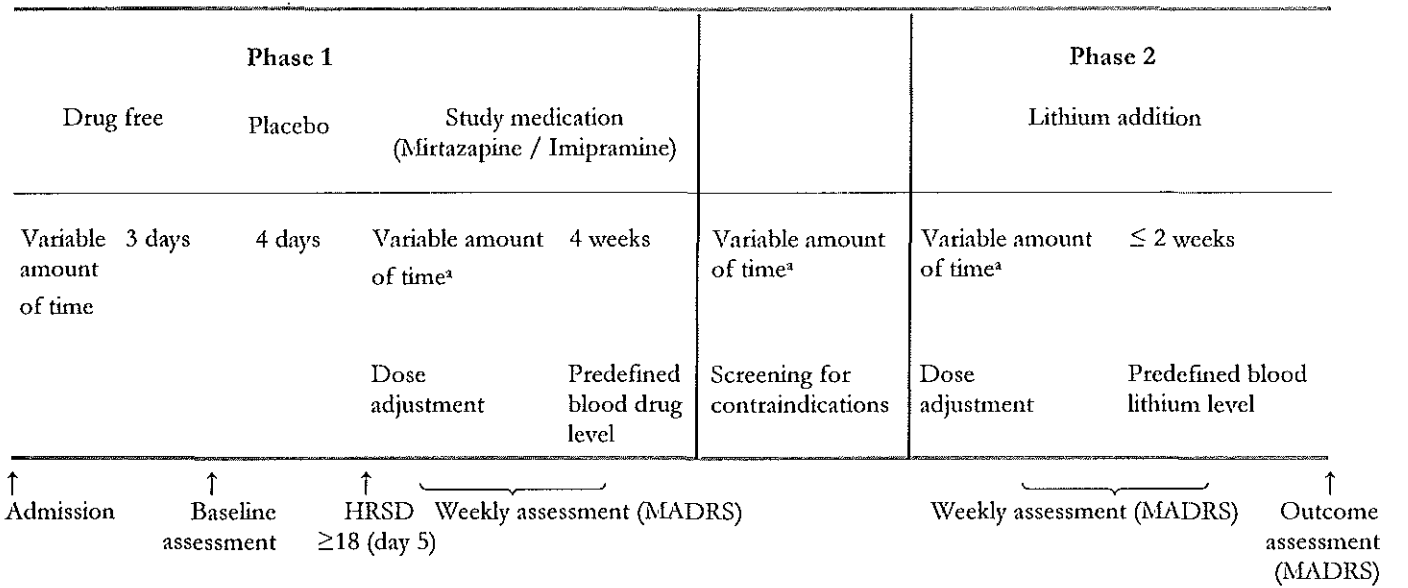
Phase 1: Double-blind study-medication period

For a detailed description of the double-blind part of the study the reader is referred to our previous report (Bruijn et al., 1996). The general outline is presented in Figure 1. The study was performed at the inpatient depression unit of the Department of Psychiatry of the University Hospital Dijkzigt Rotterdam, where uncomplicated depressed patients as well as treatment-resistant depressed patients are treated. Included were patients aged 18-65 years who had a DSM-III-R diagnosis "major depressive episode" (American Psychiatric Association), which was assessed by two psychiatrists performing the depression part of the Schedule for Affective Disorders and Schizophrenia (SADS; Spitzer and Endicott, 1977), and a Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960) score $\geq$ 18. Patients with hallucinations, schizophrenia, paranoid psychosis, organic brain syndrome, chronic drug or alcohol abuse, or clinically relevant somatic disease were excluded.

After giving written informed consent patients were randomly allocated to double-blind treatment. Treatment was started with either 75 mg/day of imipramine or 20 mg/day of mirtazapine. After 2 days, the dose was doubled unless severe side effects were observed. Blood levels were monitored weekly, and doses of both drugs were adjusted (by an independent psychiatrist to preserve blindedness) to obtain fixed blood levels (200-300 μg/l for imipramine + desmethyl-imipramine and 50-100 μg/l for mirtazapine). Response was assessed weekly with the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979). No psychotropic medication besides the study medication was allowed except for 1 to 6 tablets per day containing 45 mg of an extract of valerian in case of anxiety or insomnia. This extract was assumed to be without antidepressant effect. In exceptional cases, lorazepam, 1 to 5 mg/day, for intolerable agitation or anxiety, or haloperidol, 1 to 15 mg/day, in case of intolerable psychotic symptoms was prescribed.

Phase 2: Lithium addition period

Four weeks after attainment of the predefined blood level of mirtazapine or imipramine, non-responders had lithium added to the double-blind medication. After screening for contraindications (thyroid, cardiac, or renal disease), lithium was started at a daily dose of 200 to 800 mg at 8 p.m. After 5 to 7 days, the blood lithium level was monitored at 8 a.m., and weekly thereafter at 8 a.m. The dose was adjusted to



[a] See the section titled "Results: Patient population and dropouts"

Figure 1 General outline of the study design

obtain as soon as possible a blood level of 0.5 to 1.0 mmol/l. The effect of lithium addition was evaluated weekly by assessment with the MADRS, up to 2 weeks after reaching the blood level of 0.5 to 1.0 mmol/l. The mirtazapine/imipramine medication was kept blind throughout the trial period.

Data analysis and statistical methods

The results of the sequential treatment strategies were evaluated with survival analysis using the Cox proportional hazards model. Duration of treatment until meeting the response criterion was the survival time variable. Response was defined as a 50% or more reduction in the baseline MADRS score. During phase 1, the last time this response was assessed was at 4 weeks after attainment of the predefined blood level, unless the response criterion was met earlier. During lithium addition, the last time response was assessed at 2 weeks after attainment of the blood lithium level of 0.5 to 1.0 mmol/l, unless the response criterion was met earlier. Dropouts were censored at the time of dropout. Eventual non-responders were censored at the end of the treatment strategy, i.e., 2 weeks after attaining the blood lithium level of 0.5 to 1.0 mmol/l. As planned *a priori* (Bruijn et al., 1996), the analyses for testing differences in response rates between the 2 treatment strategies were adjusted for the following co-variables and their possible interactions with type of treatment: MADRS pre-treatment scores (baseline severity), duration of the current episode, adequate pre-treatment during current episode, number of previous depressive episodes, bipolar type, melancholic type, psychotic features, type of depression according to Research Diagnostic Criteria, and time to attain pre-defined blood level of study medication. A survival analysis with start time of haloperidol as time-dependent co-variable was performed to take into account the possible influence of haloperidol co-medication on response. Each co-variable and, consecutively, this co-variable with its interaction with type of treatment were entered in a model containing type of treatment only. A p value $< .05$ (2-sided) was considered statistically significant. Eventually, a model was fitted containing all co-variables and interactions that had thus appeared to be significant. Hazard ratios with 95% confidence intervals (CIs) are presented. The hazard ratio is the factor by which the response rate is multiplied for each unit increase in the co-variable. Thus, if the co-variable is dichotomous (e.g., treatment type), then the hazard ratio is the ratio of the response rate in one group (e.g., mirtazapine with lithium addition) relative to the other (e.g., imipramine with lithium addition).

Table 1. Total population (n = 100) (figures are number of patients, unless otherwise indicated)

Variable	Mirtazapine (n = 50)	Imipramine (n = 50)
Age: years, mean ± SD (range)	45 ± 11 (23-64)	47 ± 10 (27-65)
Sex: male/female	12/38	11/39
Diagnosis: "major depressive episode" (DSM-III-R)	50	50
* Unipolars	45	50
Non-psychotic, 1st episode	16	22
Non-psychotic, recurrent	15	14
Psychotic, 1st episode	8	10
Psychotic, recurrent	6	4
* Bipolars	5	-
Non-psychotic	4	-
Psychotic	1	-
Melancholic type	46	42
Major depressive episode (RDC)	50	49
Retarded Depression (RDC)	15	15
Agitated Depression (RDC)	16	17
Endogenous Depression (RDC)	50	47
Suicidal	25	31
HRSD-baseline, total score, mean ± SD (range)	26.3 ± 4.6 (19-37)	26.3 ± 5.08 (18-37)
MADRS-baseline, total score, mean ± SD (range)	37.6 ± 6.0 (25-51)	36.0 ± 6.9 (16-54)
Duration current episode		
< 1 year	32	30
> 1 year	18	20
Adequate pre-treatment with antidepressants	21	21
Family history (1st/2nd degree)		
Depression	27	32
Suicide	10	9
Personality disorder	10	7

Adequate pre-treatment during current episode was defined as an adequate dose of an antidepressant received for at least 4 weeks (Potter and Rudorfer, 1989).

The efficacy of lithium addition as such (the effect in phase 2) in non-responders was not analysed separately because the difference in efficacy between imipramine and mirtazapine in phase 1 makes non-responders taking imipramine and non-responders taking mirtazapine no longer representative of the same pool of patients.

Results

Patient population and dropouts

One hundred seven depressed inpatients were randomly assigned to either mirtazapine (n = 54) or imipramine (n = 53). Seven patients (4 taking mirtazapine and 3 taking imipramine) did not receive lithium addition although they were non-responders; 1 patient recovered shortly after addition of haloperidol, 1 patient was discharged without our consent, and 5 patients were continued on double-blind medication without ever receiving lithium addition. Thus, 100 patients were available for analysis (Table 1). During phase 1, 8 patients dropped out, while 2 patients were excluded from analyses because monitoring of blood levels showed non-compliance (Table 2).

Table 2. Drop-outs and non-completers by non-compliance (n = 13) during mirtazapine or imipramine monotherapy (phase 1), and during lithium addition (phase 2).

Treatment	Reason for leaving study	*N*
Mirtazapine		
Phase 1	Transfer to other ward	1
	Refuse to take medication	1
	Non-compliance (blood level ↓)	1
Phase 2	Deterioration → ECT	1
	Non-compliance	1
Imipramine		
Phase 1	Mania	1
	Orthostasis	1
	Deterioration	1
	Fever and delirium	1
	Allergic reaction	2
	Non-compliance (blood level ↓)	1
Phase 2	Discharge without our consent	1

Thus, 90 patients (47 taking mirtazapine and 43 taking imipramine) remained after phase 1. The mean ± SD time to reach the predefined blood levels was 10.9 ± 3.5 days (range 5-21) for mirtazapine and 13.6 days ± 4.6 days (range 7-25) for imipramine. Including the 4-week treatment at this blood level, the mean ± SD total period on study medication (phase 1) was 38.9 ± 3.5 days (range 33-49) for mirtazapine and 41.6 ± 4.6 days (range 35-53) for imipramine.

According to the main response criterion at 4 weeks after attaining the predefined blood level, 33 (37%) of 90 were responders and 57 (63%) of 90 were non-responders. Thus, 57 non-responders (35 taking mirtazapine and 22 taking imipramine) were started on lithium addition. Lithium was added to the study medication after a mean lag time of 3.5 days. During phase 2, no patients dropped out because of adverse effects. Three patients dropped out for other reasons: 1 taking mirtazapine was treated with electro-convulsive therapy after 10 days of lithium addition, because of worsening of the depression, and 1 patient taking imipramine was discharged without our consent after 11 days of lithium addition. A third patient had to be excluded from analyses because the monitored blood levels of mirtazapine showed non-compliance. Thus, 54 patients completed phase 2; 33 taking mirtazapine and 21 taking imipramine. The mean ± SD total period of lithium addition, including the time to reach the lithium blood level of 0.5-1.0 mmol/l, was 22.4 ± 5.0 days (range 13-32) for patients receiving mirtazapine and 23.2 ± 5.0 days (range 18-33) for those receiving imipramine.

Co-medication (Table 3)

Twenty patients received co-medication (8 received haloperidol, 3 haloperidol and lorazepam, and 9 lorazepam). Before lithium addition, lorazepam was administered to 6 patients (4 taking mirtazapine and 2 taking imipramine). Before lithium addition, 11 of the 29 psychotic patients (7 taking mirtazapine and 4 taking imipramine) were treated with between 4 and 12 mg/day of haloperidol during 9 to 40 days. Only 2 of those patients (1 taking mirtazapine and 1 taking imipramine) were responders; the other 9 were non-responders. The MADRS score after haloperidol addition with these 9 patients was the same as or higher than before haloperidol addition. Thus, none of these patients benefitted from haloperidol, and all were subsequently treated with lithium addition. One of these patients, taking imipramine, entered the lithium addition period with this co-medication, which was continued during the entire period of lithium addition.

Table 3. Number of patients receiving co-medication during mirtazapine or imipramine monotherapy (phase 1) and during lithium addition (phase 2)

	Mirtazapine	Imipramine
Lorazepam		
Phase 1	4	2
Phase 2	8	3[a]
Total	8	4
Haloperidol		
Phase 1	7	4
Phase 2	0	1[b]
Total	7	4

[a] One patient stopped taking lorazepam before entering phase 2, and 1 patient continued this co-medication.

[b] One patient who received haloperidol in phase 1 entered phase 2 with this co-medication.

Treatment effects:

Survival analyses: The survival analysis of the total patient group (n = 100) with type of treatment as independent variable showed a significant difference between the 2 treatment groups (hazard ratio = 1.75; 95% CI = 1.03 to 3.00; p = .04). The results of the survival analyses with several co-variables are presented in Table 4. The co-variables "duration of present episode", "adequate pre-treatment during current episode" and "psychotic features" showed a significant contribution to treatment results. No other co-variable was significant, although "melancholic type" approached significance (see Table 4). There were no significant interactions of co-variables with treatment, although the interaction of "psychotic features" with treatment type almost reached statistical significance (p = .06).

Next, we tested a model containing only the significant co-variables in addition to type of treatment together (Table 5, Model 1). From this model we deleted 1 co-variable with the highest p value ("adequate pre-treatment"). This led us to the final model containing the co-variables "duration of present episode" and "psychotic features" in addition to type of treatment; both co-variables did improve the precision of the estimated difference between the 2 treatment groups (Table 5, Model 2).

The probability of non-response (Kaplan-Meier curve) of the 2 treatment groups in time is shown in Figure 2.

Table 4. Results of survival-analyses comparing the two treatment strategies with each co-variable separately*

Co-variable	Hazard ration	95% Confidence interval	*p*
Baseline severity (HRSD score)	1.01	0.95-1.06	0.582
Duration of present episode (> 1 year)	0.32	0.17-0.60	0.000
Number of previous depressions	1.04	0.90-1.19	0.597
Bipolar type (yes)	1.40	0.42-4.72	0.585
Adequate pre-treatment (yes)	0.45	0.25-0.79	0.005
Melancholic type (yes)	2.40	0.86-6.96	0.093
Psychotic features (yes)	2.16	1.23-3.83	0.008
Retarded depression (RDC) (yes)	0.89	0.49-1.69	0.695
Agitated depression (RDC) (yes)	0.71	0.40-1.26	0.241
Endogenous depression (RDC) (yes)	1.89	0.44-8.08	0.390
Haloperidol (time-dependent) (yes)	1.24	0.52-2.92	0.629
Time to attain predefined blood level of antidepressant (days)	0.99	0.93-1.06	0.784

* The hazard ratio is the factor by which the response rate is multiplied for each unit increase in the co-variable.

Table 5. Two models of survival analyses comparing the 2 treatment strategies, using the significant co-variables from Table 4.

Variable	Hazard ratio	95% Confidence interval	*p*
Model 1:			
Type of treatment (imipramine)	2.04	1.18-3.51	0.010
Duration of present episode (> 1 year)	0.39	0.21-0.76	0.005
Adequate pre-treatment (yes)	0.58	0.32-1.05	0.074
Psychotic features (yes)	1.71	0.96-3.03	0.068
Model 2:			
Type of treatment (imipramine)	2.08	1.21-3.58	0.009
Duration of present episode (>1 year)	0.35	0.19-0.66	0.001
Psychotic features (yes)	1.82	1.03-3.22	0.040

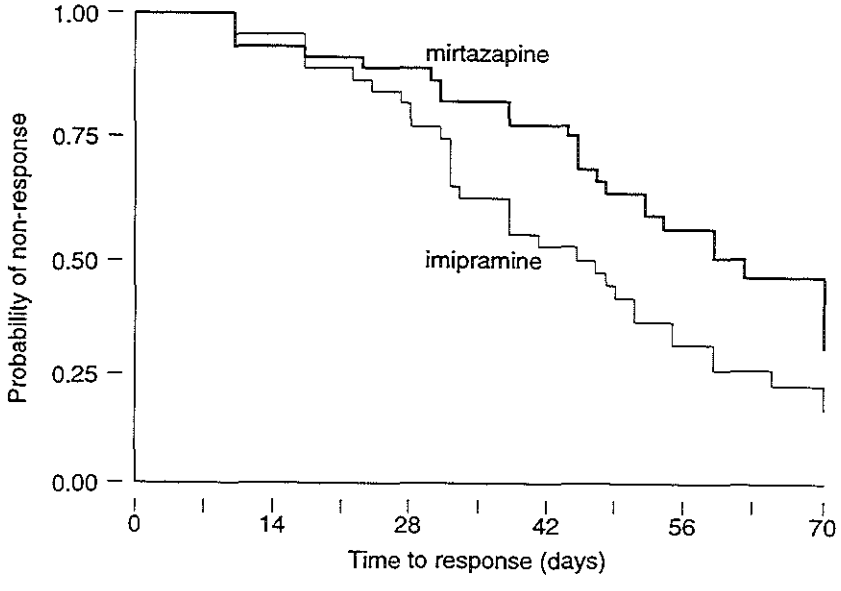


Figure 2: Probability of non-response (Kaplan-Meier curve) of the 2 treatment groups in time: Mirtazapine plus lithium addition (n = 50, bold line), and imipramine plus lithium addition (n = 50, thin line). p = 0.04

Numbers of responders: in order to obtain some insight into the contribution of each of the significant co-variables separately, the proportion and percentage of responders at the end of each treatment phase are presented in Table 6. These numbers illustrate the result of the survival analysis. Both long duration of the present episode and adequate pre-treatment are related to poor response, although as much in the imipramine group as in the mirtazapine group. It must be pointed out that these co-variables are highly related, as 26 (68%) of 38 patients with a duration of the present episode > 1 year had an adequate pre-treatment of the present episode, compared with 16 (26%) of 62 with a duration of ≤ 1 year. Table 6 also illustrates that the superiority of imipramine is more pronounced in the group of psychotic patients.

Table 6. Number and % of responders at the end of phase 1 and phase 2 by co-variables that contributed significantly to the results in the survival analysis.

	Intent-to-treat								Completers							
	Mirtazapine				Imipramine				Mirtazapine				Imipramine			
	Phase 1		Phase 2		Phase 1		Phase 2		Phase 1		Phase 2		Phase 1		Phase 2	
Variable	N	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Total group	12/50	24	24/50	48	21/50	42	32/50	64	12/45	27	24/45	52	21/42	50	32/42	76
Psychotic																
Yes	4/15	27	7/15	47	9/14	64	12/14	86	4/12	33	7/12	58	9/12	75	12/12	100
No	8/35	23	17/35	49	12/36	33	20/36	56	8/33	24	17/33	52	12/30	40	20/30	67
Duration																
≤ 1 year	9/32	28	19/32	59	18/30	60	24/30	80	9/27	33	19/27	70	18/27	67	24/27	89
> 1 year	3/18	17	5/18	28	3/20	15	8/20	40	3/18	17	5/18	28	3/15	20	8/15	53
Pre-treatment																
Not adequate	10/29	34	15/29	52	16/29	55	23/29	79	10/25	40	15/25	60	16/27	59	23/27	85
Adequate	2/21	10	9/21	43	5/21	24	9/21	43	2/20	10	9/20	45	5/15	33	9/15	60

Discussion

The purpose of the present study was to compare the overall effectiveness of a 2-step treatment strategy with a standard tricyclic antidepressant and subsequent lithium addition with a similar treatment strategy with a modern antidepressant and subsequent lithium addition. For the clinician, it is important to know which of these 2 strategies results in an optimal chance for the patient to recover in the shortest period of time. The results of the survival analysis, in which all patients started on treatment are included (intent-to-treat), indicate a significant difference in favour of imipramine and subsequent lithium addition. According to the analyses that used several baseline variables as co-variables, "duration of present episode", "adequate pre-treatment" and "psychotic features" are significant predictors for response (see Table 4). In 2 different models, these co-variables improved the precision of the estimation of the difference between the 2 treatment strategies (see Table 5).

The fact that no significant interaction between any of the 3 significant co-variables and treatment type was observed indicates that these baseline variables did not contribute significantly to the difference between the 2 treatments. Thus, both treatment strategies show less effect in patients with a duration of present episode > 1 year and in patients with adequate pre-treatment of present episode (baseline variables that often go hand in hand), as also reported in the analysis of phase 1 of this study (Bruijn et al., 1996). However, there was an almost significant interaction between the baseline variable "psychotic features" and treatment type. Thus, it is possible that psychotic patients profited more than non-psychotic patients from the superiority of imipramine. These results emphasise the value of lithium addition to tricyclics, especially for patients with psychotic depressions, as has been suggested in earlier reports (Price et al., 1983; Pai et al., 1986; Stein and Bernadt, 1993).

No other co-variables were significant in these analyses. This was especially of importance for the unequally divided baseline variable "bipolar"; the 5 bipolar patients were by chance all included in the mirtazapine group (Tables 1 and 4), but according to the analysis, this fact did not influence the response rate in the mirtazapine group.

It may be argued that the overall response was influenced by haloperidol, received by 7 patients taking mirtazapine and 4 patients taking imipramine. However, of these 11 patients, only 2 (1 taking mirtazapine and 1 taking imipramine) were responders before lithium addition, indicating that haloperidol was not instrumental in the recovery in those patients. Moreover, a survival analysis with haloperidol intake as time-dependent co-variable showed no significant contribution to the results (Table 4).

Thus, in a group of severely depressed inpatients, the treatment strategy of imipramine administration with subsequent lithium addition for non-responders is more effective than the same strategy with mirtazapine and lithium addition (76% vs. 53% responders, respectively), as is also evident from the intent-to-treat analysis (64% vs. 48% responders). The advantage of imipramine is in part offset by the higher number of treatment failures due to side effect-related dropout; during phase 1, 6 of 7 dropouts that occurred with imipramine treatment were caused by adverse effects as compared with none of 3 that occurred with mirtazapine treatment.

Most open and double-blind studies with respect to lithium addition have involved non-responders to antidepressants for which response and dropout percentages of phase 1 are not reported (Schöpf, 1989a); in fact, the antidepressants involved often were not listed. Thus, the overall effectiveness of treatment with the antidepressant and of subsequent lithium addition can not be estimated. The present results illustrate the importance of this issue: the comparison between the results of lithium addition to imipramine non-responders and to mirtazapine non-responders, respectively (i.e., analysis of the results of phase 2 without taking into account phase 1), could suggest equal efficacy of lithium addition to both antidepressants. However, this is not an appropriate comparison, since in our study mirtazapine is less effective than imipramine, and the patient populations entering the lithium addition phase are not therefore comparable.

Regarding the difference in effectiveness between mirtazapine and imipramine in phase 1, one could argue that adjusting the dose of both drugs to attain fixed blood levels could have influenced the results because this procedure is not a validated one for mirtazapine as it is for imipramine. However, the mean mirtazapine dose of 76 mg/day (range 40-100 mg) was above the dose used in other inpatient studies (Bruijn et al., 1996), which does not make probable a reduced response rate due to the fixed blood level.

It must be emphasised that our results can not be generalised to patient populations other than this group of severely ill inpatients, of whom many (29%) were psychotic. Trials similar to the present one in other patient populations are needed for further generalisation.

Taking into account the literature on the efficacy of tricyclic antidepressants in severely depressed inpatients (Bruijn et al., 1996; Danisch University Antidepressant Group, 1986, 1990) we translate our results into clinical practice as follows. We start with imipramine treatment at fixed blood levels and, if necessary, add lithium, which is sufficient and effective for the majority of patients. The risk of more common as well as more severe adverse effects is accepted, because this risk does not offset the

superior overall effectiveness of imipramine. In the case of troublesome or severe side effects the patient is shifted to a modern antidepressant such as mirtazapine without losing much time in treatment, and, if necessary, lithium is added to this antidepressant.

Drug names:

Haloperidol (Haldol and others), imipramine (Tofranil and others), lorazepam (Ativan and others), mirtazapine (Remeron).

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6 | Trait anxiety and the effect of a single high dose of diazepam in unipolar depression

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Chapter 6

TRAIT ANXIETY AND THE EFFECT OF A SINGLE HIGH DOSE OF DIAZEPAM IN UNIPOLAR DEPRESSION

Abstract

In this cross-sectional study we explored in 101 depressive inpatients (DSM-III-R) the association between level of trait anxiety and variables that have been investigated previously to discern primary and secondary depression, respectively. Besides, we explored the influence of trait anxiety level on difference in treatment response to either imipramine or mirtazapine. We found no relation between trait anxiety level and treatment response to either imipramine or mirtazapine.

The most important finding of this study is the significant differential response to the diazepam test: Depressive patients with high trait anxiety showed predominantly disappearance of depressive symptoms without sedation and depressive patients with low trait anxiety showed predominantly sedation without disappearance of depressive symptoms. The opposite response to the diazepam test in patients with a different history of trait anxiety in spite of similar depressive symptomatology is suggestive for differences in underlying pathophysiologic mechanisms.

Keywords:

Depression; Trait Anxiety; Diazepam test; MAO-activity; Neuroticism; Treatment response.

Introduction

Patients with a history of anxiety often develop a depression later in their life. This applies to anxiety disorders (Clancy et al., 1978, Dealy et al., 1981, Moras & Barlow 1992, Schatzberg et al., 1990) proper as well as to chronic anxiety symptoms not fulfilling the diagnostic criteria for anxiety disorder. Van Valkenburg et al. (1983) e.g., found differences between depressive patients with chronic lifelong nervousness preceding the onset of depression (anxiety as a trait, without having a diagnosable preceding anxiety disorder) and patients without this pre-morbid nervousness.

The concept of depression secondary to chronic anxiety may be related to the "psychasthenia" concept of Janet (Jelgersma, 1939): in addition to patients with melancholia (primary depression) he observed patients who had a lifelong vulnerability, a trait, to develop various complaints such as phobias, compulsions, doubt, shame, fear for the future, depersonalisation and fatigue.

A related concept was proposed by Akiskal (1998): "Generalised anxious temperament" (GAT) with lifelong high trait anxiety which fluctuates in reaction to stress and which can escalate to a full-blown generalised anxiety disorder. According to Akiskal, "Generalised anxiety disorder" (GAD) is in continuum with GAT. Generalised anxiety temperament may predispose to and is often associated with depression. The view of generalised anxiety being a personality trait, which can exacerbate into an anxiety disorder and which predisposes to depression, is in line with the evidence from longitudinal studies that chronic anxiety disorders are not infrequently accompanied by secondary depression, whereas chronic depression rarely is associated with a secondary anxiety disorder (Cloninger et al., 1981).

Nuller et al. (1982) reported that the reaction to the diazepam test distinguished primary depressions from depressions secondary to anxiety and predicted a good response to treatment with an antidepressant or to treatment with a benzodiazepine, respectively. We performed a cross-sectional study in depressed patients exploring clinical, personality and biological variables, which could help to distinguish patients with different levels of trait anxiety.

Material and Methods

General Outline

The study was performed on the inpatient depression unit of the Department of Psychiatry of the University Hospital "Dijkzigt" Rotterdam. Eligible patients had to be drug free for at least 3 days before baseline assessment. Included were patients aged 18-65 with a "major depressive episode" (DSM-III-R; American Psychiatric Association, 1987) with a Hamilton Rating Scale for Depression (HRSD) score ≥18 (Hamilton, 1960). Excluded were patients with schizophrenia, paranoid psychosis, organic brain syndrome, chronic drug or alcohol abuse, clinically relevant renal, hepatic, cardiovascular, or endocrine disease, presence of absolute contraindication for either imipramine or mirtazapine, and pregnancy or the risk to become pregnant. Patients were given a detailed outline of the study, following which written informed consent was obtained and a single blind placebo was administered for 4 days.

The variables to be examined because of their possible relationship with trait anxiety were neuroticism (Stavrakaki and Vargo, 1986), MAO-activity in platelets (Davidson et al., 1980), response to a single high dose of diazepam (diazepam test, Nuller et. al., 1982) and response to treatment.

At the end of the placebo period MAO-activity in platelets was measured and a provocation test with diazepam was performed, and subsequently patients were randomly allocated to double-blind treatment with either imipramine or mirtazapine. Doses of both drugs were adjusted to obtain fixed blood levels as described previously (Bruijn et al., 1996). Outcome measurement with the HRSD was performed 4 weeks after attaining this predefined adequate blood level. Response was defined *a priori* as a reduction of 50% or more of the outcome HRSD score.

Assessments

All assessments were done by one research psychiatrist (JB), except the section of the Schedule for Affective Disorders and Schizophrenia (SADS; Spitzer and Endicott, 1981), which relates to depression, which was performed in the presence of a second psychiatrist. This standardised interview was administered before the start of the placebo period to obtain RDC diagnoses (Research Diagnostic Criteria, Spitzer et al., 1978) and to assess state anxiety symptoms. Scoring was based on consensus between both psychiatrists. During the baseline period there was an interview with the partner or a first degree relative of the patient to evaluate the patients history of possible anxiety disorders administering a questionnaire which comprised the SADS questions on anxiety disorders (to identify patients with a history of anxiety disorders), and to assess the level of trait anxiety, using a questionnaire with 34 questions pertaining to trait anxiety. These questions on trait anxiety were both related to aspects of psychic anxiety (e.g., nervousness, anxious feelings, fear of dying, irritability, impatience, concentration disturbances, depersonalisation, indecisiveness) and to aspects of somatic anxiety (e.g., restlessness, trembling, muscle tension, insomnia, shortness of breath, chest pain, palpitations, abdominal distress, dizziness, sweating). Presence as well as intensity and frequency of items were quantified (score of each question: 0-4, i.e., absent, mild, moderate, severe; range of total score: 0 - 136).

MAO-activity (μmol/l/hour) was measured in whole blood with kynuramine as the substrate (Van Kempen et al., 1985) and calculated per platelet. The diazepam test was applied according to Nuller et al. (1982) by giving 40 mg diazepam by

Table 1. Patient population (n = 101): Relation between trait anxiety sum score (TA, mean ± SD) and other variables*

Categorical variables Comparison of differences regarding TA per variable.		Number*	Trait anxiety	p-value (univariate)
Sex: Male		23	23 ± 17	.18
Female		78	18 ± 16	
DSM-III-R diagnosis				
Psychotic:	Yes	30	16 ± 13	.25
	No	71	21 ± 17	
Recurrent:	Yes	40	24 ± 15	.02
	No	61	17 ± 16	
Melancholic type	Yes	86	20 ± 17	.90
	No	15	18 ± 14	
Retarded depression (RDC)	Yes	30	20 ± 16	.44
	No	71	18 ± 18	
Agitated depression (RDC)	Yes	34	20 ± 15	.77
	No	67	19 ± 17	
Endogenous depression (RDC)	Yes	97	19 ± 16	.80
	No	4	17 ± 18	
Suicidal	Yes	56	22 ± 17	.03
	No	45	16 ± 15	
Duration current episode	> 1 year	39	16 ± 14	.16
	≤ 1 year	62	21 ± 17	
Benzodiazepine use before admittance during current episode	Yes	52	22 ± 17	.09
	No	49	16 ± 15	
History of one or more anxiety disorders (RDC)	Yes	11	35 ± 23	.01
	No	90	18 ± 14	

Table 1 continues

Table 1 (continued) Patient population (n = 101): Relation between trait anxiety sum score (TA, mean ± SD) and other variables*

Categorical variables Comparison of differences regarding TA per variable	Number*	Trait anxiety	p-value (univariate)
Diazepam test			
Negative	36	13 ± 11	.005
Intermediate	28	19 ± 19	
Positive	36	25 ± 16	
Outcome measurement 50% response			
Responders with mirtazapine	11/47 (23%)		
Responders with imipramine	23/45 (51%)		
Interaction Medication / Trait Anxiety	not sign.(p=.32)		
Numeric variables Spearman Rank correlation with trait anxiety	Mean ± SD (range)	Coeff.	p-value
Age	47 ± 11 (23-65)	.158	.11
Age of onset of first depression	40 ± 12 (16-63)	-.010	.92
HRSD baseline	26 ± 5 (18-37)	.093	.36
Sum score trait anxiety questionnaire (TA)	19 ± 16 (0-67)	- - -	- -
Sum score state anxiety symptoms (SADS)	21 ± 5 (6-36)	.110	.27
MAO-activity: µmol/l/10⁹platelets*hr	11 ± .05 (.03-.26)	.027	.80
Neuroticism score (ABV)	68 ± 32 (13-123)	.106	.31
Outcome measurement HRSD score:			
HRSD score after mirtazapine	19± 9 (1-34)	.044	.77
HRSD score after imipramine	14± 9 (1-32)	.179	.24
Interaction Medication / Trait Anxiety	not sign. (p = .64)		

* Data for some patients are missing.

rectiole. At baseline and 1 and 4 hours after administration of diazepam the reaction of the patient to the diazepam test was assessed by scoring 7 items from the Comprehensive Psychiatric Rating Scale (CPRS, Åsberg and Perris, 1978): observed sadness, psychic anxiety, somatic anxiety, pessimistic thoughts, observed affect, somnolence. There were 3 possible clinical reactions:

1) *Negative:* Symptoms like observed sadness and pessimistic thoughts underwent no change and there was pronounced somnolence for several hours from which awakening was difficult.

2) *Intermediate*: Incomplete reduction of observed sadness and pessimistic thoughts and varying degrees of somnolence from which awakening was not difficult.

3) *Positive*: Complete disappearance of all symptoms, sometimes with euphoria, without any somnolence, this reaction persisting for several to 24 hours.

To quantify neuroticism the 'Amsterdamse Biografische Vragenlijst' (ABV; Wilde, 1970) was administered when the depression was in remission to minimise the chance of measuring 'state' instead of the intended measurement of the 'trait'. For all patients this assessment was made in the period from shortly before discharge until 3 months after discharge.

Data analysis and statistical methods

The Kolmogorov-Smirnov goodness of fit test was performed to test normality of the distribution of all continuous variables. Independent samples *t*-tests or one way ANOVA's were used on variables approximately normally distributed and otherwise Mann-Whitney tests or Kruskal-Wallis tests were performed. To analyse the relationship between the sum score of the trait anxiety questionnaire and other continuous variables Spearman rankorder correlations were applied.

The relationship between trait anxiety and the diazepam test was analysed with multiple linear regression analysis in order to adjust for possibly confounding variables (Table 1). For this purpose all variables which showed differences regarding trait anxiety level with a significance level $< .20$ were kept in the regression model after backward elimination, and the variable "sum score of state anxiety symptoms" was always entered to control for state anxiety. In the regression

model which was performed to calculate the adjusted means of the trait anxiety sum scores in the 3 diazepam test groups, the co-variables were set at their mean value.

To analyse the possible influence of the level of trait anxiety on the difference in treatment response to either mirtazapine or imipramine, multiple linear regression analysis was performed with the outcome HRSD score as dependent continuous variable and study medication, the sum score on the trait anxiety questionnaire and its interaction with study medication as independent variables. Similarly, logistic regression analysis was performed with the 50% responders as dependent dichotomous variable. All tests were performed two-sided. Each analysis was performed with all available data excluding missing data per analysis.

Ethical considerations

The protocol was approved by the Ethics Committee of the University Hospital "Dijkzigt" and of the Medical Faculty of the University of Rotterdam.

Results

Patient population

One hundred and one unipolar depressed inpatients were included (Table 1). Data were missing for some patients as outlined in Table 2; data were complete for 77 of the 101 patients.

The relation between trait anxiety and other variables

Table 1 shows the patient characteristics at baseline and the univariate relation between each of the variables and trait anxiety. The sum score of the trait anxiety questionnaire was significantly higher in "recurrent" versus "single episode", "suicidal" versus "not suicidal" and "history of one or more anxiety disorders" versus "no history of anxiety disorders". There was no significant correlation between the sum score of the trait anxiety questionnaire and the total score of anxiety symptoms (SADS) during the depressive episode (state anxiety), MAO-activity, and neuroticism score, respectively. Regression analyses with the HRSD score and logistic regression analyses with the 50% responders showed no significant interaction with study medication ($p = 0.64$ and $p = 0.32$, respectively). Thus, the level of trait anxiety appeared to have no relation to the difference in treatment response with mirtazapine or imipramine, respectively.

Table 2. Reasons for missing data (n = 24); in some subjects more than one variable was missing

Variable	n	Reason
MAO-activity missing	12	Logistic
Diazepam test missing	1	Refusal
Neuroticism (ABV) missing	7	Logistic (3), refusal (3), treatment-resistant (1)
Dropout mirtazapine treatment	2	Refusal (1), non-compliance (1)
Dropout imipramine treatment	7	Deterioration (1), non-compliance (1), side effects (5)

A significant positive relation was found between the sum score of the trait anxiety questionnaire and response in the diazepam test (Table 1, one way ANOVA: p = 0.005). This seems to be a robust finding, because after adjusting for possible confounding variables the relation between trait anxiety level and the response to the diazepam test remained significant (p = 0.022, Tables 3 and 4).

There was no significant relation between the sum scores of state anxiety symptoms (SADS) and the results of the diazepam test (Tables 3 and 5).

Table 3. Results of a multiple regression analysis (n = 100) concerning the relation between trait anxiety level and the results of the diazepam test, adjusted for possibly confounding factors.

Variables	Coefficiënt (B)	Standard error (SE)	Significance (p)
Constant	- 4.90	13.08	
Sex (female)	- 6.16	3.60	0.090
Psychotic (yes)	- 5.16	3.33	0.130
Suicidal (yes)	8.72	3.17	**0.007**
Duration current episode (> 1 year)	- 5.48	3.06	0.076
Benzodiazepine use before admittance During current episode (yes)	6.52	2.93	**0.029**
Diazepam test:			
Negative	0		}
Intermediate	6.81	3.66	} **0.022**
Positive	9.42	3.47	}
Age (year)	0.37	0.14	**0.009**
Sum score state anxiety symptoms (SADS)	0.38	0.31	0.222

Table 4. Mean sum score of trait anxiety questionnaire in the 3 diazepam test groups unadjusted and adjusted for possible confounding factors (see Table 3)

Diazepam test result (n)		Mean trait anxiety sum score (SE)			
		Unadjusted		Adjusted	
Negative	(36)	13.33 (2.56)		13.82 (2.40)	
Intermediate	(28)	18.57 (3.87)	$p = .005$	20.63 (2.76)	$p = .022$
Positive	(36)	25.33 (3.62)		23.24 (2.44)	

Table 5. Mean sum scores of the state anxiety symptoms (SADS) in the 3 diazepam test groups

Diazepam test	Sum score of state anxiety symptoms Mean ± SD (range)
Negative	21 ± 6 (6-36)
Intermediate	20 ± 5 (13-30)
Positive	22 ± 4 (15-31)

Discussion

In this study we explored the relation of level of trait anxiety in depressive patients to neuroticism score, age of onset of first depression, reaction to diazepam test, MAO activity in platelets, and response to different antidepressants. We found no significant relation between trait anxiety and each of these factors except for the results of the diazepam test. A high trait anxiety level correlated with a positive response to the diazepam test and a low trait anxiety level with a negative response to diazepam.

There was no correlation between neuroticism scores and trait anxiety level. The neuroticism score may have been biased by the depressive state, as has been observed before (Svrakic and Cloninger, 1994). The significant correlation (p = 0.04) between the outcome HRSD score and the neuroticism score done shortly after the treatment period points to such a bias. Thus, a possible relation between neuroticism and trait anxiety may have been obscured by the depressive state.

We did not reproduce the results of Davidson et al. (1980) who found higher MAO activity in platelets of patients with depression secondary to anxiety disorders

than in platelets of patients with primary depression. It is possible that MAO activity is more related to the level of state anxiety symptoms than to trait anxiety (Thase and Howland, 1995). The level of state anxiety symptoms differed between the groups of primary and secondary depressions in the study by Davidson (1980) but not between patients with high trait anxiety and patients with low trait anxiety in ours.

The most important finding of this study is the relation between trait anxiety level and the reaction to the diazepam test. Thus, depressive patients with high trait anxiety showed predominantly disappearance of depressive symptoms without sedation and depressive patients with low trait anxiety showed predominantly sedation (somnolence) to the high dose of diazepam used in the test. These results can not be explained by differences in state anxiety, because there were no significant differences between high trait anxiety patients and low trait anxiety patients regarding anxiety symptomatology during depression (sum scores of the state anxiety items (Table 1); an analysis adjusting for this variable and other possible confounding variables did not weaken the relation between trait anxiety level and the diazepam test (Tables 3 and 4) and the subgroups of the diazepam test showed no differences in mean sum scores of the state anxiety items (Table 5).

The only clinical variables in our patient group which showed significant differences regarding trait anxiety were "suicidality" and "recurrent depression" (Table 1), hinting at a more severe and recurrent character of depressions with a high trait anxiety level. This finding is in line with the literature on patients with coexistent anxiety and depressive syndromes, which indicates that there is increased chronicity of the illness and a poorer prognosis (Stavrakaki and Vargo, 1986). However, there are no other obvious symptomatological differences between depressive patients with high trait anxiety and low trait anxiety in our patient group.

The fact that patients with a different history of trait anxiety and similar depressive symptomatology show a totally opposite response to the diazepam test is suggestive for differences in underlying pathophysiologic mechanisms. Although this is not to infer from current symptomatology, depressive patients with high trait anxiety may be more aroused than depressive patients with low trait anxiety.

Townsend et al. (1998) reported a heightened autonomic arousal evidenced by cardiovascular measures in patients with major depressive disorder secondary to a panic disorder compared to patients with primary major depressive disorder. Akiskal (1985) reported greater arousal in patients with anxiety disorders as well as in patients with depressions secondary to anxiety compared to patients with primary

depressions. He suggests that anxiety, even when complicated by depression, is psychophysiologically a distinct disorder from primary depression.

In conclusion, the results of the present study show differences in response to diazepam in patients with high versus low trait anxiety. The results are in line with the postulates of Janet (Jelgersma, 1939) and Akiskal (1998) on the differences between primary depressions and depressions secondary to anxiety, respectively.

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7 Discussion

Chapter 7

Discussion

The main aim of this study was (1) to compare the efficacy of mirtazapine to the efficacy of imipramine, a standard treatment, among inpatients with major depressive disorder, including patients with melancholic features, with psychotic features, with suicidality, with treatment resistance and with relatively long duration of the current episode of depression. We hypothesised that a high trait anxiety level would be predictive for response to mirtazapine and that a low trait anxiety level would be predictive for response to imipramine in this patient group. In addition to the comparison of mirtazapine and imipramine in the total study population, and the investigation of the possible relation between trait anxiety level and response, more specifically the following issues were investigated: (2) the efficacy of treatment in psychotic depressed patients compared to non-psychotic patients in the total study population as well as in the two treatment groups separately; (3) the overall efficacy of the treatment strategy: mirtazapine and subsequently lithium addition for non-responders to mirtazapine alone, compared to the efficacy of treatment strategy: imipramine and subsequently lithium addition for non-responders to imipramine alone; (4) the value of certain clinical, personality and biological variables in distinguishing patients with different levels of trait anxiety. In the previous chapters, these specific issues have been extensively introduced, described, and discussed. The purpose of this final chapter is to integrate the results from these parts of the study, to discuss the findings and clinical implications of the study, and finally to discuss recommendations for future research.

Summary of results

(1) *Difference in efficacy between mirtazapine and imipramine.* In the total study population of the present study there was a considerable difference in antidepressive efficacy between the new antidepressant mirtazapine and the standard TCA imipramine (Chapter 2, Figure 2A) in favour of the last. This difference was significant according to all *a priori* defined outcome criteria.

(2) *Differences in response patterns.* In addition, we found differences in response patterns between the two drugs (Chapter 4, Figures 3 and 4). Imipramine was more effective than mirtazapine for symptoms such as depression, guilt and retardation, and it had an effect on all of the symptoms, which progressively increased during treatment. Mirtazapine, on the other hand, had a more restricted effect on sleep and anxiety symptoms, to which tolerance developed.

(3) *Psychotic depressed patients.* The difference in efficacy between mirtazapine and imipramine was even more pronounced in the subgroup of psychotic depressed patients (Chapter 2, Figure 2B). In the patients who were treated with imipramine without adjuvant antipsychotic medication, a high response rate of approximately 70% was observed in the psychotic depressed patients.

(4) *Lithium addition.* The efficacy of imipramine and subsequent lithium addition for non-responders was superior to mirtazapine followed by lithium addition in non-responders (Chapter 5, Figure 1), indicating that patients who are starting treatment with an antidepressant and who are treated with lithium addition to that antidepressant in case of non-response, have a higher probability to recover and also recover sooner when started on imipramine.

(5) *Trait anxiety.* No relation was found between trait anxiety level and treatment response to either imipramine or mirtazapine. Our hypothesis that mirtazapine, an antidepressant with supposed strong anxiolytic properties, would be more effective in patients with a high trait anxiety level and that the standard antidepressant imipramine would be more effective in patients with a low trait anxiety level, was not confirmed. In addition, no variables were found which could help to distinguish patients with different levels of trait anxiety, except for the diazepam test.

Why did we detect differences not found before?

Mirtazapine compared to imipramine

The most important finding in the present study is the considerable difference in efficacy between mirtazapine and imipramine. In addition, we found significant differences in the response patterns between the two drugs. Such differences between antidepressants have not been reported before, both in two other studies comparing mirtazapine to TCAs in inpatients (Zivkov and De Jongh, 1995; Richou et al., 1995), and in most studies with SSRIs and other newer antidepressants compared to TCAs in inpatients (Kellams et al., 1979; Feighner, 1980; Gershon et al., 1981; Guelfi et al., 1992; Benkert et al., 1996; Anderson, 2000).

Why did we detect these differences which have not been found before? There are a number of differences regarding selection of study population, and regarding methodological issues including dose design, use of concomitant psychotropic medication and dropout rate between the present study and other studies.

(1) *Study population.* The study population of the present study comprised severely depressed inpatients with typical inpatient characteristics, including suicidality, melancholic and/or psychotic features, and long duration and/or adequate pre-treatment with an antidepressant during the current episode. As described in Chapter 1, the study population of the two other inpatient studies on mirtazapine (Richou et al., 1995; Zivkov and De Jongh, 1995) were different. Suicidal patients, psychotic depressed patients, and patients with long duration of the current episode were excluded in these studies, while it was not clear whether the patients in these studies had melancholic features. The characteristics of patients in these study populations are more similar to those of outpatients than of inpatients. That is, they are not suicidal, and not psychotic, and have a duration of the current episode no longer than six months. To test the efficacy of antidepressants in inpatients it is essential that study populations include patients with typical inpatient characteristics. It is important to describe study populations in terms of these characteristics (Chapter 2, Table 1), because they appear to have more weight in predicting response than severity defined by the total HRSD score (Anderson, 2000). The placebo response rates in patients with a long duration of the current episode, patients with melancholic features and patients with psychotic features, are usually low (Angst et al., 1989; Peselow et al., 1992; Schatzberg and Rothschild, 1992), which makes the finding of true drug/drug differences more probable (Angst et al., 1989).

(2) *Dose design.* Comparison studies with TCAs such as imipramine are technically difficult to perform due to the narrow therapeutic and tolerability ranges of these drugs (Burke and Preskorn, 1995). If the study permits gradual titration of the dose, as in a flexible dose design, most patients on TCAs will finish on doses that are too low to test the efficacy of these drugs. The reason is that many patients simply cannot or will not tolerate such doses. The majority of studies comparing SSRIs or newer antidepressants to TCAs in inpatients were performed with a flexible dose design (Kellams et al., 1979; Feigner, 1980; Gershon et al., 1981; Guelfi et al., 1992; Zivkov and De Jongh, 1995; Richou et al., 1995; Anderson, 2000). With some TCAs, for instance clomipramine, a fixed dose design may result in a therapeutic blood level for most patients (DUAG, 1986; DUAG, 1990; DUAG, 1993). However, a daily dose of 200 mg imipramine, as in the study of Benkert et al. (1996), will result in a

therapeutic blood level of imipramine in only 60% of patients (Glassman et al., 1977). Moleman et al. (1996) have shown that no fixed dose of imipramine will result in more than 30% of the patients treated with that fixed dose having a therapeutic blood level and not having an unacceptable risk of having toxic side effects. If a study calls for aggressive dosing of the TCA as in a fixed dose design with a higher dose, then there will be a large dropout rate, undermining the adequacy of the test of efficacy of the TCA. Thus, it is not surprising that there are compelling data to suggest that response rates to TCAs can be markedly increased by adjusting drug dose based on blood level determinations (Glassman et al., 1977; Reisby et al., 1977; Perry et al., 1994). In the present study, adjusting of the dose to a predefined fixed blood level resulted in a mean daily dose of imipramine of 235.5 mg with a very wide range (37.5 – 450 mg). No fewer than 9 (20%) patients were on a daily dose of 112.5 mg or less, and 17 (37%) patients received 300 mg imipramine or more. It is unlikely that such doses would have been administered without blood level control. One could argue that this dose design is less suitable for mirtazapine because adjusting the dose to a predefined blood level is not a validated procedure. In fact, therapeutic blood levels of mirtazapine are not known. This indeed is one of the limitations of the present study. However, we do not believe that this really is a problem in our study, as the dose adjustments in the present study, based on predefined blood levels of mirtazapine, resulted in a mean dose of 76 mg/day, which is higher than the mean dose in previous inpatient mirtazapine studies: 47 mg/day (Richou et al., 1995), and 53 mg/day (Zivkov and De Jongh, 1995). In addition, there are no data suggesting that mirtazapine has a curvilinear blood level response curve, as is the case with nortriptyline (Åsberg, 1974), and there were not many dropouts in the present study, which could have been another drawback of a possible high dose.

(3) *Concomitant psychotropic medication.* It has been suggested that concomitant medication with benzodiazepines may mask differences in efficacy between antidepressants (Angst, 1993), and this certainly would apply to our findings regarding symptom clusters involving sleep and anxiety (Chapter 4), which have given us more insight in the specific properties of the tested drugs. As discussed in Chapter 1, in most inpatient studies concomitant psychotropic medication is permitted, probably because restriction of these drugs is practically difficult. However, with the intensive support of trained nurses as in the present study it is feasible: only a minority of patients was treated with anxiolytic, hypnotic or sedative concomitant medication, and the difference in efficacy between mirtazapine and imipramine remained significant if these patients were excluded.

(4) *Dropout rate.* A high dropout rate may bias results of clinical trials even if analyses are based on "intent to treat" samples (Angst et al., 1989; Chapter 1). The dropout rate in the present study was low (9.1%). The previous studies with mirtazapine including inpatients had higher dropout rates (17 – 30%). Evidence-Based Mental Health states that a dropout rate higher than 20% is not acceptable in clinical trials (Anonymous, 2000). One of the reasons for the low dropout rate in the present study may be the adjustment of the dose to therapeutic blood levels preventing dropout as a result of side effects by too high blood levels of the drug (Burke and Preskorn, 1995). In addition, special attention and training has been allocated to staff at all levels of the research-ward where the present trial was conducted, to ensure proper medical and psychological care for the patients.

In conclusion, the combination of the methodological strengths regarding study population, dose design, concomitant medication and dropout rate appear to have resulted in the finding of true drug/drug differences which otherwise might have been missed. Adjustment of the dose to therapeutic blood levels seems to be the most important aspect in this respect. Burke and Preskorn (1995) and Sanathanan and Peck (1991) suggested performing such a trial appears to be very efficient due to the large inter-individual variability in plasma drug concentration of TCAs at a given dose. The few studies, which also showed significant differences in efficacy between the tested drugs, were all performed with therapeutic blood levels of the TCA involved in most patients (DUAG, 1986, 1990, 1993; Roose et al., 1994). DUAG applied a fixed dose design of 150 mg daily of the reference TCA clomipramine with blood plasma control afterwards. This design resulted, perhaps by chance, in a therapeutic blood level for most patients. Roose et al. (1994) applied a dose design with adjustment of the nortriptyline dose to therapeutic blood levels, but this study was not randomised. Thus, the present study is the first double-blind randomised controlled trial with dose adjustment of imipramine to therapeutic blood levels. It is not surprising this being the first such trial, because a plasma controlled trial with any drug class is difficult to perform especially under double-blind conditions (Sanathanan and Peck, 1991; Johnson and Holt, 1995). However, the present study shows that such trials are feasible in severely depressed inpatients, but similar methodology has also been applied in a long term trial on preventive treatment of bipolar patients (Moleman et al., 2000).

Psychotic depressed patients

The difference in efficacy between mirtazapine and imipramine in the present study was even more pronounced in the subgroup of psychotic depressed patients (Chapter 2, Figure 2B). In the mirtazapine group there was no significant difference in efficacy between the psychotic and the non-psychotic patients. However, the patients who were treated with imipramine without adjuvant antipsychotic medication, a high response rate of approximately 70% was observed in the psychotic depressed patients against a response rate of about 40% in the non-psychotic patients. As discussed in Chapter 3, this result was contrary to most studies on the treatment of psychotic depressed patients (Glassman et al., 1975; Spiker et al., 1985; Chan et al., 1987; Parker et al., 1992; Schatzberg and Rothschild, 1992). A major difference between the present study versus other studies on the pharmacotherapy of psychotic depressed patients was the treatment of all patients with therapeutic blood levels for a sufficient long period in the present study. Differences in patient characteristics between the study populations may also play a role. In our study, the psychotic depressed patients had a shorter duration of the current episode, and this feature may have contributed significantly to the more favourable response of the psychotic patients. Nevertheless, an analysis adjusting for this co-variable showed an even more pronounced difference between psychotic and non-psychotic patients in their response to imipramine (Chapter 3, Figure 2). Another difference between the present study and other studies was that in the present study all psychotic patients had mood congruent delusions, while in some other studies patients with mood incongruent delusions may have been included, although this is not always clearly described (Spiker et al., 1985; Chan et al., 1987; Kocsis et al., 1990; Schatzberg and Rothschild, 1992). Psychotic depressed patients with mood incongruent delusions are less likely to respond to treatment with antidepressants alone compared to combination therapy of antidepressant and antipsychotic medication (May et al., 1990; Parker et al., 1992).

Lithium addition

The efficacy of imipramine and subsequent lithium addition for non-responders was superior to mirtazapine followed by lithium addition in non-responders (Chapter 5, Figure 1). This is the first study comparing the overall effectiveness of two treatment strategies with lithium addition for non-responders As discussed in Chapter 5 most open and double-blind studies with respect to lithium addition comprised non-responders to antidepressants for which response and dropout

percentages of the preceding antidepressant phase were not reported (Schöpf, 1989; Austin et al., 1991; Bauer and Döpfmer, 1999). Thus, the overall effectiveness of treatment with the antidepressant and subsequent lithium addition in case of non-response can not be estimated. The present results illustrate the importance of this issue: the comparison between the results of lithium addition to imipramine non-responders and to mirtazapine non-responders, respectively (i.e., analysis of the results of lithium addition phase without taking into account the results of the preceding antidepressant phase), could suggest equal efficacy of lithium addition to both antidepressants. However, this is not an appropriate comparison, since in our study mirtazapine is less effective than imipramine, and the patient populations entering the lithium addition phase are, therefore, not comparable.

Clinical implications

(1) *To which depressed inpatients do the results apply?* The results apply to unipolar depressed inpatients with typical inpatient characteristics such as suicidality, melancholic and psychotic features, long duration of the current episode and/or adequate pre-treatment with an antidepressant during the current episode. In other studies patients with these characteristics were excluded. Thus, our study more so than other studies seems to reflect the typical depressed inpatient population. However, it is stressed that it is unknown to what extend the findings of the present study can be generalised, because the study population was restricted to one centre. These results can not be applied to bipolar depressed patients in view of the low number of these patients in the present study and in view of the different recommendations for acute bipolar depression (Halpern and Glassman, 1990; Nolen and Bloemkolk, in press).

(2) *Which is the treatment of choice for unipolar depressed inpatients?* The present study shows a considerable difference in antidepressant efficacy between the newer antidepressant mirtazapine and the standard antidepressant imipramine in inpatients. Adding the results of the present study to the results of studies on the efficacy of the SSRIs and the newer antidepressants as reviewed in Chapter 1, it can be concluded that treatment with a TCA with dose adjustment to therapeutic blood levels is the treatment of choice for unipolar depressed inpatients, because this treatment is most evidence based and probably the most effective pharmacotherapy in depressed inpatients. This result is remarkable because since the introduction of imipramine as an antidepressant (Kuhn, 1958), many new antidepressants came to the market.

Considering the difference between mirtazapine and imipramine in the present study, no supportive evidence was found for the suggestion that inpatients can be effectively treated with mirtazapine because of its "dual action" properties (Kasper, 1997; Hirschfeld, 1999; Montgomery, 1999; Möller, 2000). Compared to imipramine, no rapid onset of action of mirtazapine was found as suggested by Montgomery (1999). The apparent rapid onset of action of mirtazapine in the present study was explained by the temporary stronger anxiolytic effect of this drug (Chapter 4, Figures 3 and 4).

Although the investigators did not systematically rate side effects, only in some dropout patients specific treatment for side effects was necessary according to the observations of treating psychiatrists and nurses. The dropout rates regarding side effects were low 5/53 (9%) for imipramine compared to 0/54 (0%) for mirtazapine. Although this is a non-significant difference, these results do not rule out that the tolerability of mirtazapine is somewhat better than of imipramine. However, the intention to treat analysis taking into account all dropouts resulted in a significant difference of the overall efficacy in favour of imipramine. Thus, the lower efficacy of mirtazapine is not offset by the better tolerability of this drug.

In the light of these findings it is remarkable that, in contrast to the Dutch guidelines for treatment of depression (De Groot, 1995; Birkenhäger and Moleman, 1998; Nolen and Hoogduin, 1998), the official guidelines of the American Psychiatric Association (APA, 2000) and of the British Association of Psychopharmacology (Anderson et al., 2000) do not mention explicitly the superiority of TCAs at therapeutic blood levels for inpatients.

(3) *Which is the place of lithium addition?* The present study shows superiority of imipramine plus lithium addition. Regarding the question whether the lithium addition effect is limited to any class of antidepressant, to date no sufficient information is available (Bauer and Döpfmer, 1999). Most double-blind studies concerning lithium addition were performed on TCAs, and there are only few data available of double-blind placebo controlled studies concerning lithium addition to SSRIs or other newer antidepressants in inpatients (Schöpf, 1989; Katona et al., 1995; Austin et al., 1991; Baumann et al., 1996; Bauer and Döpfmer, 1999). The results of the present study emphasise the value of lithium addition to tricyclics, especially for patients with mood congruent psychotic depressions, as has been suggested in earlier reports (Price et al., 1983; Pai et al., 1986; Stein and Bernadt, 1993). Although this has to be tested as yet, lithium addition to a TCA may be a good alternative for the combination of an antidepressant and an antipsychotic in the

treatment of these patients. While the Dutch guidelines advocate the addition of lithium to a TCA in the light of the available data, it is remarkable that the US and UK guidelines advocate lithium addition in case of non-response without mentioning to which antidepressant lithium should be added.

Recommendations for future research

In view of the design and the results of the present study, it is essential to perform double-blind randomised studies with dose adjustment of, at least, the reference drug to therapeutic blood levels, and with control of use of concomitant psychotropic medication and dropout rate among large inpatient samples that are representative of inpatients. Actually, the same principles also apply to outpatient groups. These aspects minimise the chance of type-2 error and maximise the probability to detect true drug/drug differences. The persistent lack of trials with such a methodology may ultimately lead to more and more antidepressants being used in certain groups of depressed patients although they in fact are less effective than the classical drugs in these patients. We perform or will perform similar studies comparing other antidepressants such as an SSRI and for instance venlafaxine to TCAs in our inpatient groups.

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Summary

Summary

This thesis is concerned with the pharmacotherapy of inpatients with a major depressive disorder. In *Chapter 1* the background of the present study is given. Successively, epidemiological aspects of unipolar depression, evidence on the efficacy of various classes of antidepressants in inpatients, lithium addition in treatment resistant depressive patients, and trait anxiety level as a possible predictor of response are discussed.

In many studies comparing a new antidepressant with a tricyclic antidepressant (TCA), the statistical "no difference" conclusion has been taken as an indication of therapeutic equivalence with the TCA. In the majority of studies, however, a possible difference in efficacy between the drugs may have stayed undetected as a result of methodological shortcomings and/or a too low statistical power by too small sample size. One of the methodological problems is the dose design of many studies. Dosing of TCAs without blood level control will not result in an adequate blood level of the antidepressant in 30%-50% of the patients. In a dose design without blood level control, flexible dosing of TCAs is more problematic than fixed dosing because disturbing side effects could result in doses below the therapeutic level, which may lead to response rates below the real potentials of these drugs. The majority of trials comparing antidepressants used a flexible dose design without blood level control. This may have lowered the efficacy of the TCAs used in these trials, which implicates that real differences between TCAs and other antidepressants may have been missed. Another problem is the study population of many inpatient studies. Patients with typical inpatient characteristics were often excluded in these studies. The characteristics in these study populations are more similar to those of outpatients than of inpatients. In view of the selection of these patient groups, it is unlikely that the results of these studies could be generalised to other inpatient groups with typical inpatient characteristics such as melancholic features, psychotic features, suicidality, treatment resistance and a relatively long duration of the current episode of depression.

Given the low number of studies on the newer antidepressants in inpatients and given the methodological weaknesses of most of these studies, the efficacy of these drugs compared to the TCAs in inpatients is still uncertain.

In addition to the issue regarding the optimal antidepressant treatment, there is the question with respect to the strategy in treatment resistant depressive patients. Lithium addition appears to be an effective strategy in patients with treatment-

resistant depression. The treatment with an antidepressant and the addition of lithium, however, are often regarded separate, unrelated treatment decisions. Thus, in prescribing an antidepressant, the efficacy of possible lithium addition to that specific antidepressant is not taken into account. Therefore, comparison of the overall effectiveness of treatment strategies of different antidepressants and subsequent lithium addition of the respective non-responders is of interest.

Predictors of response, which would be useful in identifying patients who would best be treated with a certain antidepressant, have been scarcely established. Patients with a history of (trait) anxiety often develop a depression later in their life, which may be phenomenologically similar to depressions of patients without a history of anxiety. Disorders with different aetiology may show differential response to specific treatments. Therefore, it may be useful to explore the predictive value of trait anxiety in depressive patients with respect to the specific response to different antidepressants.

The main purpose of the present study was to compare the efficacy of mirtazapine, a new antidepressant with supposed strong anxiolytic properties, to the efficacy of imipramine, a standard TCA, among inpatients with a major depressive disorder, including patients with typical inpatient characteristics. The subgroup of psychotic depressed patients is of particular interest because these patients have been reported to show a weak response to treatment with antidepressants alone. A randomised controlled clinical trial was performed, which was designed to avoid methodological problems such as inadequate dosing of the reference drug, a high dropout rate and concomitant treatment with other psychotropic drugs. Thus, the purpose of this design was to minimise the chance of type-2 errors and to maximise the chance to observe quantitative and qualitative differences between the treatment outcomes of the two drugs.

The specific aims of this study, as stated *a priori* in the study protocol, were the following:

Primary aims: (1) To compare the efficacy of mirtazapine and imipramine in inpatients with major depressive disorder. (2) To determine the value of trait anxiety level as a predictor for response to mirtazapine and impramine, respectively.

Secondary aims: (3) To compare the efficacy of treatment of psychotic depressed patients with that of non-psychotic depressed patients in the total study population and in the mirtazapine and the imipramine group, respectively. (4) To compare the overall efficacy of two treatment strategies for depressed inpatients: mirtazapine and subsequently lithium addition for non-responders, or imipramine and subsequently lithium addition for non-responders (not stated *a priori*). (5) To determine clinical,

personality and biological variables which could help to distinguish patients with different levels of trait anxiety.

In *Chapter 2*, the pharmacological properties of mirtazapine are discussed. Subsequently, the design of this randomised, double blind study with inpatients and the selected patient population, are described in detail. Patients with a DSM-III-R diagnosis of major depression and a Hamilton (17-item) score of $\geq$ 18 were selected. After a drug-free and a placebo washout period of 7 days in total, 107 patients still fulfilling the HRSD criterion of $\geq$ 18 started on active treatment. The dose was adjusted to a predefined fixed blood level to avoid sub-optimal dosing of imipramine. In the total study population, after 4 weeks' treatment on the predefined blood level, there was a considerable difference in antidepressive efficacy between mirtazapine and imipramine in favour of the last. This difference was significant according to all *a priori* defined outcome criteria. The subgroup of psychotic patients showed an even larger superiority of imipramine over mirtazapine, response percentages being around 60-70% for imipramine and around 20-30% for mirtazapine, depending on the analysis performed. Most of these results were significant, even with the small number of psychotic patients studied. These results are discussed in the light of the data on this issue from the literature and in the light of the applied methodology.

In *Chapter 3*, we focus on the response to imipramine in a group of patients with psychotic depression and compare this to patients without psychotic features. Most studies report a poor response of psychotic depressed patients to tricyclic antidepressants in comparison with non-psychotic depressed patients and in comparison with treatment with tricyclic antidepressants in combination with antipsychotics. However, the issue of optimal treatment of psychotic depressed patients has not been resolved as yet. Our aim in presenting these findings was to contribute to the discussion on the optimal treatment of psychotic depressed patients. Fifty-two patients with a unipolar major depression, comprising 15 patients with mood-congruent psychotic features and 37 with no psychotic features, were commenced on treatment with imipramine. After 4 weeks of treatment on predetermined blood level, a high response rate of 69% (9/13 completers) was observed in our patients with psychotic depression who were treated with imipramine with no adjuvant antipsychotic medication. This contrasted with a much lower response rate of 43% (14/32 completers) to the same treatment in our non-psychotic patients. Throughout the entire treatment period the steeper response

curve of the psychotic depressed patients in the present study was clear. Possible confounding factors did not account for this result. Most reports in the literature conclude that combination of an antidepressant with an antipsychotic is the treatment of choice in psychotic depressed patients in view of the poor response to mono-therapy with an antidepressant. In our patient group, however, the first choice treatment is mono-therapy with imipramine with blood level control because of the high success rate, the more so since subsequent lithium addition for psychotic depressed patients with unsatisfactory response increased the response rate from 69% to 100%. Differences with data from the literature on this issue are discussed and possible causes of these differences are evaluated.

In *Chapter 4*, the results of an analysis of different symptom clusters and their course during treatment with mirtazapine and imipramine, respectively, are reported. Total HRSD scores and 7 symptom clusters were analysed in the 85/107 patients (79%) who were not receiving any co-medication. Imipramine was more effective for symptoms such as depression, guilt, and retardation, which can be regarded as the core symptoms of depression and it had an effect on all of the symptoms, which progressively increased during treatment. Mirtazapine, on the other hand, had a more restricted effect on sleep and anxiety symptoms, to which tolerance developed. Differences in response patterns have not previously been observed in studies comparing antidepressants, despite the wealth of such studies and numerous efforts to discover differences between antidepressants. These findings suggest that mirtazapine may have anxiolytic and sedative properties and fewer antidepressant properties than imipramine in severely depressed inpatients. The implications of these results with respect to possible differences in mechanism of action between the two drugs are discussed.

In *Chapter 5*, the comparison of 2 treatment strategies for depressed inpatients is reported: mirtazapine (phase 1) and subsequently lithium addition for non-responders (phase 2) or imipramine (phase 1) and subsequently lithium addition for non-responders (phase 2). The design of phase 2 of the study is described in detail. Non-responders had lithium added to the double-blind mirtazapine or imipramine medication. The dose was adjusted to obtain a blood level of 0.5 to 1.0 mmol/l. Treatment effects were evaluated weekly by the Montgomery-Åsberg Depression Rating Scale (MADRS) for up to 2 weeks on this lithium blood level. A survival analysis of the total patient group intent-to-treat showed a significant difference in favour of the treatment strategy with imipramine and subsequent lithium addition,

indicating that patients who are starting treatment with an antidepressant and who are treated with lithium addition to that antidepressant in case of non-response, have a higher probability to recover and also recover sooner when started on imipramine.

In *Chapter 6* the results of our analysis of the value of trait anxiety level as a predictor for response to mirtazapine and imipramine, respectively, are described. No relation was found between trait anxiety level and treatment response to either imipramine or mirtazapine. Our hypothesis that mirtazapine, an antidepressant with supposed strong anxiolytic properties, would be more effective in patients with a high trait anxiety level and that the standard antidepressant imipramine would be more effective in patients with a low trait anxiety level, was not confirmed. In addition, no variables were found which could help to distinguish patients with different levels of trait anxiety, except for the diazepam test. The most important finding of this part of the study is the significant differential response to the diazepam test in the 101 unipolar patients: Depressive patients with high trait anxiety showed predominantly disappearance of depressive symptoms without sedation and depressive patients with low trait anxiety showed predominantly sedation without disappearance of depressive symptoms. The opposite response to the diazepam test in patients with a different history of trait anxiety in spite of similar depressive symptomatology is suggestive for differences in underlying pathophysiologic mechanisms.

In *Chapter 7*, the results of the study and clinical implications are discussed, and finally, recommendations for future research are given.

The most important finding in the present study is the considerable difference in efficacy between mirtazapine and imipramine. This difference was even more pronounced in the subgroup of psychotic depressed patients. In addition, we found significant differences in the response patterns between the two drugs. Such differences between antidepressants have not been reported before. The combination of the methodological strengths regarding study population, dose design, concomitant medication, and dropout rate appear to have resulted in the finding of true drug/drug differences which otherwise might have been missed. Adjustment of the dose to therapeutic blood levels seems to be the most important aspect in this respect. Such a dose design appears to be very efficient due to the large inter-individual variability in blood level of TCAs at a given dose.

These results apply to unipolar depressed inpatients with typical inpatient characteristics such as suicidality, melancholic and psychotic features, long duration

of the current episode and/or adequate pre-treatment with an antidepressant during the current episode. Adding the results of the present study to the results of studies on the efficacy of the Selective Serotonin Reuptake Inhibitors (SSRIs) and the newer antidepressants as reviewed in Chapter 1, it can be concluded that treatment with a TCA with dose adjustment to therapeutic plasma levels is the treatment of choice for unipolar depressed inpatients, because this treatment is most evidence based and probably the most effective pharmacotherapy in depressed inpatients. The results of the present study emphasise the value of lithium addition to tricyclics in case of non-response, especially for patients with mood congruent psychotic depressions, as has been suggested in earlier reports.

In view of the design and the results of the present study, it is essential to perform more double-blind, randomised studies with dose adjustment of, at least, the reference drug to therapeutic plasma levels, and with control of use of concomitant psychotropic medication and dropout rate among large inpatient samples that are representative of inpatients. Actually, the same principles also apply to outpatient groups. These aspects minimise the chance of type-2 error and maximise the probability to detect true drug/drug differences. The persistent lack of trials with such a methodology may ultimately lead to more and more antidepressants being used in certain groups of depressed patients although they in fact are less effective than the classical drugs in these patients.

Samenvatting

Samenvatting

Dit proefschrift gaat over de farmacotherapie van opgenomen patiënten met een depressieve stoornis. In *hoofdstuk 1* wordt de achtergrond van dit onderzoek gepresenteerd. Achtereenvolgens worden besproken: epidemiologische aspecten van unipolaire depressie, het bewijsmateriaal betreffende de effectiviteit van verschillende soorten antidepressiva bij opgenomen patiënten, lithiumadditie bij therapieresistente depressieve patiënten en het "trait anxiety" niveau als mogelijke voorspeller van respons.

In veel onderzoeken, waarin een nieuw antidepressivum met een tricyclisch antidepressivum (TCA) werd vergeleken, heeft men aangenomen dat de statistische "geen verschil"-conclusie een teken is van therapeutische gelijkwaardigheid tussen het TCA en het nieuwe antidepressivum. Bij het merendeel van deze onderzoeken echter, kan een mogelijk verschil in effectiviteit tussen de middelen onontdekt gebleven zijn ten gevolge van methodologische tekortkomingen en/of een te kleine statistische "power" door een te klein aantal patiënten. Eén van de methodologische problemen in veel onderzoeken is het doseringsschema. Het doseren van TCAs zonder bloedspiegelcontrole resulteert in 30% tot 50% van de patiënten niet in een adequate bloedspiegel van het antidepressivum. Bij een doseringsschema zonder bloedspiegelcontrole geeft flexibel doseren meer problemen dan doseren met een vaste dosis, omdat hinderlijke bijwerkingen zouden kunnen resulteren in subtherapeutische doseringen, hetgeen kan leiden tot responspercentages die lager liggen dan de werkelijke mogelijkheden van deze middelen. Bij de meeste onderzoeken, waarbij de effectiviteit van verschillende antidepressiva wordt vergeleken, wordt gewerkt met flexibele doseringen zonder bloedspiegelcontrole. Dit kan de gemeten effectiviteit van de bij deze onderzoeken gebruikte TCAs verminderd hebben, hetgeen betekent dat in werkelijkheid bestaande verschillen tussen TCAs en andere antidepressiva onopgemerkt gebleven zijn. Een tweede probleem is de onderzoekspopulatie van veel onderzoeken bij opgenomen patiënten. Patiënten met kenmerken die juist vaak voorkomen bij opgenomen patiënten werden vaak uitgesloten bij deze onderzoeken. Derhalve is het onwaarschijnlijk, dat de resultaten van deze onderzoeken gegeneraliseerd kunnen worden ten aanzien van andere patiëntengroepen met typische eigenschappen van opgenomen patiënten

zoals vitale kenmerken, psychotische kenmerken, suïcidaliteit, therapieresistentie en een relatief lange duur van de aanwezige depressieve episode.

Gezien het geringe aantal onderzoeken met nieuwere antidepressiva bij opgenomen patiënten en gezien de methodologische tekortkomingen van de meeste van deze onderzoeken, is de effectiviteit van deze middelen bij opgenomen patiënten in vergelijking met de TCAs nog onzeker.

Naast het probleem betreffende de optimale antidepressieve behandeling is er ook de kwestie van het beleid bij therapieresistente depressieve patiënten. Lithiumadditie blijkt een effectieve aanpak te zijn bij deze patiënten. De behandeling met een antidepressivum en de additie van lithium worden echter vaak gezien als los van elkaar staande behandelingsbeslissingen. Dat wil zeggen dat men de effectiviteit van lithiumadditie bij een bepaald antidepressivum in geval van non-respons niet mee laat wegen bij de keuze van een antidepressivum. Vergelijking van de totale effectiviteit van behandelingsstrategieën met verschillende antidepressiva en daaropvolgende lithiumadditie bij de respectievelijke non-responders is daarom van belang.

Er zijn nauwelijks factoren bekend, die respons voorspellen en die van nut zouden kunnen zijn bij het vaststellen welke patiënten men het best met een bepaald antidepressivum kan behandelen. Patiënten met (trait) angst in de voorgeschiedenis ontwikkelen later in hun leven vaak een depressie die qua verschijningsvorm hetzelfde kan zijn als depressies van patiënten zonder angst in de voorgeschiedenis. Desondanks reageren stoornissen met verschillende etiologie misschien verschillend op bepaalde behandelingen. Het lijkt dan ook zinvol om bij depressieve patiënten te onderzoeken of het "trait anxiety"-niveau de specifieke respons op verschillende antidepressiva kan voorspellen.

Het belangrijkste doel van dit onderzoek was om, bij een groep opgenomen depressieve patiënten met de typische klinische kenmerken die bij die groep horen, de effectiviteit van mirtazapine, een nieuw antidepressivum met naar aangenomen wordt sterk anxiolytische eigenschappen, te vergelijken met de effectiviteit van imipramine, een standaard TCA. De subgroep van depressieve patiënten met psychotische kenmerken is hierbij van speciaal belang, omdat deze patiënten volgens de literatuur slecht zouden reageren op behandeling met antidepressiva alleen. Wij voerden een gecontroleerd gerandomiseerd klinisch onderzoek uit, dat qua opzet tot doel had zo veel mogelijk methodologische problemen te voorkomen, zoals inadequaat doseren van het referentiemiddel, een hoog percentage uitvallers en comedicatie met psychotrope middelen. Het was dus de bedoeling om de kans op type-2 errors zo klein mogelijk te maken en om de kans op het vinden van kwantitatieve

en kwalitatieve verschillen tussen de behandelingsresultaten van de twee middelen zo groot mogelijk te maken.

Meer specifiek gesteld waren de doelen van dit onderzoek, zoals *a priori* omschreven in het onderzoeksprotocol, de volgende:

Primaire doelen: (1) Het vergelijken van de effectiviteit van mirtazapine en imipramine bij opgenomen patiënten met een depressieve stoornis. (2) Het bepalen van de voorspellende waarde van "trait anxiety"-niveau voor respons op respectievelijk mirtazapine en imipramine.

Secundaire doelen: (3) Het vergelijken van de effectiviteit van de behandeling bij depressieve patiënten mét psychotische kenmerken met die bij depressieve patiënten zónder psychotische kenmerken in de totale onderzoeksgroep en in de respectievelijke mirtazapine- en imipramine-groep afzonderlijk. (4) Het vergelijken van de totale effectiviteit van twee behandelingsstrategieën voor opgenomen depressieve patiënten: mirtazapine en vervolgens lithiumadditie bij de non-responders of imipramine en vervolgens lithiumadditie bij de non-responders (niet *a priori* beschreven). (5) Het bepalen van klinische, persoonlijkheids- en biologische variabelen, die misschien van nut zouden kunnen zijn bij het onderscheiden van patiënten met verschillend "trait anxiety"-niveau.

In *hoofdstuk 2* worden de farmacologische eigenschappen van mirtazapine besproken. Vervolgens worden de opzet van dit gerandomiseerde dubbelblinde onderzoek en de geselecteerde onderzoekspopulatie gedétailleerd beschreven. Ingesloten werden patiënten met een DSM-III-R diagnose "depressieve episode" en een Hamilton Rating Scale for Depression (HRSD, 17-item) score van $\geq$ 18. Na een medicatievrije en placeboperiode van in totaal 7 dagen kregen 107 patiënten, die nog steeds voldeden aan het insluitingscriterium van een HRSD score van $\geq$ 18, onderzoeksmedicatie voorgeschreven. De dosis werd aangepast om een tevoren bepaalde therapeutische bloedspiegel te bereiken en zo een te lage dosering van imipramine te voorkomen. Na 4 weken behandeling op therapeutische bloedspiegels bleek imipramine in de totale onderzoekspopulatie aanmerkelijk effectiever te zijn dan mirtazapine. Dit verschil was significant volgens alle *a priori* bepaalde responscriteria. In de subgroep van de psychotische patiënten was het verschil tussen imipramine en mirtazapine nog groter, met responspercentages van rond de 60% tot 70% voor imipramine en rond de 20%-30% voor mirtazapine, afhankelijk van de uitgevoerde analyse. De meeste van deze resultaten waren significant, ondanks het kleine aantal psychotische patiënten waarom het hier ging. Deze resultaten werden

besproken in het licht van de gegevens op dit gebied uit de literatuur en in het licht van de toegepaste methodologie.

Hoofdstuk 3 gaat over de respons op imipramine bij psychotisch depressieve patiënten in vergelijking met patiënten zonder psychotische kenmerken. De meeste onderzoekers rapporteren een slechte respons van psychotisch depressieve patiënten op TCAs vergeleken met niet-psychotisch depressieve patiënten en vergeleken met behandeling met TCAs in combinatie met antipsychotica. De kwestie van de optimale behandeling van psychotisch depressieve patiënten is echter nog niet opgelost. Ons doel met het presenteren van deze resultaten was om bij te dragen aan de discussie over de optimale behandeling van psychotisch depressieve patiënten. Tweeënvijftig patiënten met een unipolaire depressie, waaronder 15 psychotische patiënten met stemmingscongruente wanen en 37 patiënten zonder psychotische kenmerken, werden behandeld met imipramine. Na 4 weken behandeling op therapeutische bloedspiegels was er een hoog responspercentage bij 69% (9/13 "completers") van de psychotische patiënten die werden behandeld met imipramine zonder toevoeging van antipsychotische medicatie. Dit stond in contrast tot het veel lagere respons percentage van 43 % (14/32 "completers") op dezelfde behandeling bij de niet-psychotische patiënten. Gedurende de gehele behandeling was de steilere responscurve van de psychotische patiënten duidelijk. Dit resultaat bleek niet te wijten te zijn aan invloed van mogelijke verstorende variabelen. De meeste onderzoeksverslagen in de literatuur concluderen, dat combinatie van een antidepressivum met een antipsychoticum de behandeling van eerste keus is bij psychotisch depressieve patiënten. In onze patiëntengroep echter is, vanwege het hoge responspercentage, de eerste keus behandeling monotherapie met imipramine onder bloedspiegelcontrole. Dit geldt des te meer gezien het feit dat de vervolgens toegepaste lithiumadditie bij psychotisch depressieve patiënten met onvoldoende reactie op imipramine het responspercentage verhoogde van 69% naar 100%. De verschillen met de gegevens in de literatuur over dit onderwerp worden besproken en mogelijke oorzaken van deze verschillen worden geëvalueerd.

In *hoofdstuk 4* wordt een onderzoeksverslag gegeven van een analyse van verschillende symptoomclusters en hun beloop tijdens behandeling met respectievelijk mirtazapine en imipramine. De totale HRSD scores en 7 symptoomclusters werden geanalyseerd bij de 85/107 patiënten (79%) die geen co-medicatie voorgeschreven hadden gekregen. Imipramine was effectiever bij

symptomen zoals depressie, schuldgevoel en psychomotore remming; symptomen die beschouwd kunnen worden als de kernsymptomen van de depressieve stoornis. Daarnaast beïnvloedde imipramine alle symptomen, hetgeen progressief toenam gedurende de behandeling. Het effect van mirtazapine, aan de andere kant, beperkte zich meer tot slaap- en angstsymptomen, maar hiervoor ontstond tolerantie. Verschillen in responspatronen werden niet eerder waargenomen in onderzoeken waarbij antidepressiva werden vergeleken ondanks de overvloed aan zulke onderzoeken en ondanks de talloze pogingen om verschillen tussen antidepressiva te ontdekken. Deze bevindingen suggereren dat mirtazapine bij ernstig depressieve patiënten misschien anxiolytische en sedatieve eigenschappen heeft en in mindere mate antidepressieve eigenschappen dan imipramine. De implicaties van deze resultaten voor de theorie over de mogelijke verschillen in werkingsmechanisme tussen de twee middelen worden besproken.

In *hoofdstuk 5* wordt een onderzoeksverslag gegeven van de vergelijking van 2 behandelingsstrategieën voor opgenomen depressieve patiënten: mirtazapine (fase 1) en vervolgens lithiumadditie voor non-responders (fase 2) of imipramine (fase 1) en vervolgens lithiumadditie voor non-responders (fase 2). De opzet van fase 2 van het onderzoek wordt gedétailleerd beschreven. Bij non-responders werd lithium toegevoegd aan de dubbelblinde mirtazapine- of imipramine-medicatie. De dosis werd aangepast om een bloedspiegel van 0.5 tot 1.0 mmol/l te bereiken. De behandelingseffecten werden wekelijks gemeten met de Montgomery-Åsberg Depression Rating Scale (MADRS) totdat de patiënt 2 weken behandeld was op deze lithium-bloedspiegel. Een survival-analyse van de totale patiëntengroep (intent-to-treat) toonde een significant verschil ten gunste van de behandelingsstrategie met imipramine en vervolgens lithiumadditie, ten teken dat patiënten, die beginnen met een antidepressivum en daar in geval van non-response lithium aan toegevoegd krijgen, een grotere kans hebben om te genezen en ook sneller genezen wanneer zij imipramine voorgeschreven krijgen.

In *hoofdstuk 6* worden de resultaten beschreven van het onderzoek naar de voorspellende waarde van het "trait anxiety"-niveau voor respons op respectievelijk mirtazapine en imipramine. Er werd geen relatie gevonden tussen "trait anxiety"-niveau en behandelingsrespons op mirtazapine of imipramine. Onze hypothese dat mirtazapine, een antidepressivum met naar men aanneemt sterk anxiolytische eigenschappen, effectiever zou zijn bij patiënten met een hoog "trait anxiety"-niveau

en dat het standaard antidepressivum imipramine effectiever zou zijn bij patiënten met een laag "trait anxiety"-niveau, werd niet bevestigd. Bovendien werden geen variabelen gevonden die van nut zouden kunnen zijn bij het onderscheiden van patiënten met verschillend "trait anxiety"-niveau, met uitzondering van de diazepam-test. De belangrijkste bevinding van dit deel van het onderzoek is de significant verschillende respons op de diazepam-test in de 101 unipolaire patiënten. Hierbij werd eenmalig een hoge dosis diazepam toegediend. Depressieve patiënten met een hoog "trait anxiety"-niveau vertoonden voornamelijk een verdwijnen van de depressieve symptomen zonder sedatie en depressieve patiënten met een laag "trait anxiety"-niveau vertoonden voornamelijk sedatie zonder verdwijnen van de depressieve symptomen. De tegengestelde reactie op de diazepam-test bij patiënten met een verschillende voorgeschiedenis wat betreft "trait anxiety", ondanks gelijkende depressieve symptomatologie, suggereert verschillen in onderliggende pathofysiologische mechanismen.

In *hoofdtuk 7* worden de resultaten van het onderzoek en de klinische implicaties ervan besproken en tenslotte worden aanbevelingen gedaan voor toekomstig onderzoek.

De belangrijkste bevinding bij dit onderzoek is het aanmerkelijke verschil in effectiviteit tussen mirtazapine en imipramine in de totale groep van opgenomen depressieve patiënten Dit verschil was nog groter in de subgroep van psychotisch depressieve patiënten. Bovendien vonden wij significante verschillen in respons-patronen tussen de twee middelen. Dit soort verschillen tussen antidepressiva werd niet eerder gerapporteerd. De combinatie van een aantal sterke methodologische aspecten wat betreft onderzoekspopulatie, doseringsschema, co-medicatie en uitvallerspercentage lijkt geresulteerd te hebben in het vinden van werkelijke verschillen tussen de middelen, die anders misschien onopgemerkt gebleven zouden zijn. Het aanpassen van de dosis totdat therapeutische bloedspiegels bereikt zijn, lijkt wat dit betreft het belangrijkste aspect te zijn. Een dergelijk doseringsschema blijkt zeer efficiënt te zijn vanwege de grote interindividuele spreiding van bloedspiegels van TCAs bij een bepaalde dosering.

Deze resultaten zijn van toepassing op opgenomen unipolair depressieve patiënten met de typische klinische kenmerken die deze patiënten vaak hebben, zoals suïcidaliteit, vitale en psychotische kenmerken, lange duur van de huidige depressieve episode en/of adequate voorbehandeling met een antidepressivum gedurende de huidige depressieve episode. Wanneer wij de resultaten van dit onderzoek voegen bij

de resultaten van de in hoofdstuk 1 besproken onderzoeken naar de effectiviteit van SSRIs en de nieuwere antidepressiva dan kunnen wij concluderen, dat behandeling met een TCA op therapeutische bloedspiegels de behandeling van eerste keuze is voor opgenomen unipolair depressieve patiënten, omdat deze behandeling het meest "evidence based" is en waarschijnlijk de meest effectieve farmacotherapie voor deze patiëntengroep. De resultaten van deze studie benadrukken de waarde van lithiumadditie bij TCAs in geval van non-respons, speciaal bij patiënten met een stemmingscongruente psychotische depressie, zoals dat ook al in eerdere onderzoeksverslagen naar voren is gekomen.

Gezien de opzet en de resultaten van dit onderzoek is het essentieel dat er meer dubbelblinde gerandomiseerde onderzoeken komen met behandeling op therapeutische bloedspiegels van tenminste het referentiemiddel en met controle van de co-medicatie en het uitvallerspercentage onder grote groepen opgenomen depressieve patiënten met klinische kenmerken, die representatief zijn voor deze groep patiënten. Eigenlijk gelden dezelfde onderzoeksprincipes ook voor ambulante patiënten. Deze aspecten maken de kans op type-2 errors zo klein mogelijk en de kans dat er in werkelijkheid bestaande verschillen tussen middelen worden gevonden zo groot mogelijk. Wanneer het tekort aan onderzoeken met een dergelijke methodologie voortduurt, zal dit bij bepaalde groepen depressieve patiënten uiteindelijk misschien leiden tot het gebruik van steeds meer verschillende antidepressiva, die bij deze patiënten eigenlijk minder effectief zijn dan de klassieke middelen.

Dankwoord

Curriculum Vitae

Dankwoord

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Curriculum Vitae

De auteur werd geboren op 9 oktober 1948 te 's-Gravenhage. In 1967 behaalde hij het gymnasium-ß diploma aan het Christelijk Gymnasium "Sorghvliet" te 's-Gravenhage. Vervolgens studeerde hij gedurende één jaar economie aan de Nederlandse Economische Hogeschool te Rotterdam. Vanaf 1968 studeerde hij geneeskunde aan de Erasmus Universiteit Rotterdam. Het artsexamen werd behaald op 21 maart 1975. Van 1975 tot 1976 volgde hij de huisartsenopleiding aan het Rotterdams Universitair Huisartsen Instituut (Opleiders: J.A.I. van Doorn en Dr.J.D. Taams). Hierna vervulde hij gedurende één jaar de militaire dienstplicht. Na de officiersopleiding bij de Geneeskundige troepen functioneerde hij als districts-psychiater (Locatie: Hoyel kazerne te Utrecht). Van 1977 tot 1978 was hij als huisarts gevestigd te Capelle aan den IJssel in associatie met H.S. Cohen.

Op 1 augustus 1978 begon hij zijn opleiding tot psychiater. In dat kader deed hij eerst een stage Neurologie op de afdeling Neurologie van het Academisch Ziekenhuis Rotterdam-Dijkzigt (hoofd: Prof. dr. A. Staal), gevolgd door de basisopleiding Psychiatrie in datzelfde ziekenhuis (opleider: Prof. dr. G.A. Ladee). Hierna volgde een keuzejaar kinderpsychiatrie in het AMC te Amsterdam (opleider: Prof. dr. D.J. de Levita). Hij werd ingeschreven in het specialistenregister op 1 september 1982. Hierna werkte hij nog enige tijd op de afdeling Kinderpsychiatrie van de GGD te Amsterdam. Sinds 1983 is hij als psychiater verbonden aan de afdeling Psychiatrie van het AZR-Dijkzigt te Rotterdam (hoofd: Prof. dr. W.J. Schudel). In 1990 werd hij hier benoemd tot chef de clinique en plaatsvervangend A-opleider. Het onderzoek dat geleid heeft tot dit proefschrift werd uitgevoerd op deze afdeling. Na de opleiding tot psychoanalyticus is hij sinds 1990 lid van de Nederlandse Vereniging voor Psychoanalyse.

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