TREATMENT OF DEPRESSED INPATIENTS

Efficacy and tolerability of a four-step treatment algorithm

Tom K. Birkenhäger
en
Walter W. van den Broek

TREATMENT OF DEPRESSED INPATIENTS

Efficacy and tolerability of a four-step treatment algorithm

DE BEHANDELING VAN OPGENOMEN DEPRESSIEVE PATIËNTEN

Effectiviteit en veiligheid van een behandelschema

Tom K. Birkenhäger
en
Walter W. van den Broek

Birkenhäger, Tom Kasper
Broek, Walter William van den
Treatment of Depressed Inpatients. Efficacy and tolerability of a four-step treatment algorithm.
Thesis, Erasmus University Rotterdam. With summary in Dutch.
Lay-out: Tini Zaanen
ISBN 90-9018069-9

The study reported in this thesis was performed at the Department of Psychiatry, Erasmus Medical Center / Erasmus University Rotterdam, The Netherlands.

Printed by Ridderprint BV, Ridderkerk, The Netherlands.

Treatment of Depressed Inpatients
Efficacy and tolerability of a four-step treatment algorithm

De behandeling van opgenomen depressieve patiënten
Effectiviteit en veiligheid van een behandelschema

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam op gezag van de
Rector Magnificus

Prof. dr. S.W.J. Lamberts

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

Woensdag 16 juni 2004 om 14.00
door

Tom Kasper Birkenhäger
geboren te Amsterdam

Walter William van den Broek
geboren te Wassenaar

Promotiecommissie

Promotoren:	Prof. dr. M.W. Hengeveld Prof. dr. P. Moleman
Overige leden	Prof. dr. W. A Nolen Prof. dr. A.H.J. Danser Prof. dr. J. Klein
Copromotor:	Dr. J.A. Bruijn

Contents **p**

1 Introduction

Chapter 1

Introduction

General introduction

The aim of the work presented in this thesis was to study various aspects of the treatment of depressed inpatients. Many antidepressants have been developed during the last decades and most of these are so-called "me too drugs". This phrase refers to the fact that many of these compounds are very similar to other antidepressants which are already on the market. The choice of a particular antidepressant is usually based on clinical experience with that compound or on other non evidence based criteria of which personal preference is one (Bruijn et al., 1999; Guscott and Grof, 1991; Nolen and Haffmans, 1989; Potter et al., 1991).

Epidemiology of depression

Community studies generally show a high prevalence of depression in different countries.

Estimations of the so-called point prevalence (the number of people meeting the criteria of the disorder at a certain moment in time) ranges from 5 to 7.5% (Ormel and Sytema, 1999).

The one-year prevalence of major depressive disorder in the USA ranges from 3% in the Epidemiological Catchment Area Study (Regier et al., 1993) to 10% in the National Co-morbidity Study (Kessler et al., 1994). The Dutch NEMESIS study (Bijl et al., 1997) shows a 5.8% one-year prevalence of DSM-III major depression in the Netherlands, the disorder being twice as prevalent in women. The lifetime prevalence of depression in the Netherlands is 15% (Bijl et al., 1997). The lifetime prevalence of depression in the USA ranges from 5 to 17% (Kessler et al., 1994).

In the Netherlands, in 1997, the prevalence of depressed patients referred to psychiatric outpatient and inpatient departments was 0.65% and 0.14%, respectively. Evidently, relatively few patients suffering from depression are referred by their general practitioner to psychiatric services. Out of 58 depressed patients identified in the NEMESIS study, on average 40 are recognised as suffering from depression by their general practitioner, and on average 6.5 are referred to a psychiatric outpatient department and on average 1.4 are treated as inpatients.

Diagnosis and Classification of depression

The core symptoms of depression are depressed mood and a lack of interest or pleasure in daily activities (anhedonia). Several additional features may be present, including lack of concentration, inappropriate guilt feelings, suicidal thoughts, psychomotor retardation or agitation and loss of libido. A diurnal variation, e.g. the symptoms are worse in the morning, may be present.

A major problem is to clearly distinguish depression from non-pathological sadness. A depressive mood can be considered pathological if it is present every day during several consecutive weeks.

Depressive disorders have been subdivided in many ways. These classifications were often based on both symptomatology and etiological assumptions. This resulted in subtypes that were strongly related, for example "endogenous depression" and "melancholia".

During the 1980s the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) gained general acceptance, more or less ending the confusion that had existed until then.

In the studies presented here, the DSM-IV criteria for depressive disorders have been used. The DSM is an a-theoretical classification system which represents psychiatric disorders as discrete conditions, characterised by the presence of a number of symptoms, without theoretical assumptions concerning etiology or course of the disorder. The classification "major depressive disorder" is part of the section "mood disorders". Within the "mood disorders" section it is important to distinguish between unipolar depression and bipolar depression. A patient suffering from a major depressive episode, who previously experienced a (hypo) manic episode, is classified as having bipolar depression.

Subclassification of a Major Depressive Episode is possible as follows:

1. Severity
2. Course (chronic, first episode, recurrence, remission)
3. Presence of catatonic features
4. Presence of melancholic features
5. Presence of psychotic features
6. Presence of atypical features
7. Onset post-partum

Melancholic features:

Definition: fulfilling the criteria for a major depressive episode and:

1) Either lack of pleasure from daily activities or lack of mood reactivity.
2) At least three of the following symptoms:
   - Distinct quality of mood (the depressive mood is experienced as being different from e.g. that of grief)
   - Diurnal variation of mood (worse in the morning)
   - Early morning awakening (at least two hours earlier than usual)
   - Obvious psychomotor retardation or agitation
   - Significant loss of appetite or weight loss
   - Inappropriate guilt feelings

The subclassification "major depressive episode with melancholic features" is very similar to the long-standing terms "melancholia" and "endogenous depression". It has been assumed that a diagnosis of melancholia or endogenous depression implies a biological rather than a psychosocial etiology of depression. Melancholia is considered particularly responsive to treatment with antidepressants. However, the prognostic value of melancholic features remains unclear, possibly because there is considerable variation in the definition of melancholic features between the various editions of the DSM.

Although the response to antidepressants may not differ from nonmelancholics, the "true drug response" (i.e. the antidepressant-placebo difference) appears to be greater in patients with melancholic features (Peselow et al., 1992). Moreover, the melancholic subtype of depression is more common in hospitalized depressive patients than in outpatients: 76% versus 40% (Stage et al., 1998).

Finally, tricyclic antidepressants (TCAs) appear to be consistently more effective than selective serotonin reuptake inhibitors (SSRIs) in patients with melancholic depression (Perry, 1996).

Psychotic features:

According to the DSM-IV criteria psychotic features can only be present during a major depressive episode if that episode is severe, which means that more symptoms are present than required for the general classification and symptoms obviously interfere with psychosocial functioning. When either delusions or hallucinations are present it is necessary to specify whether or not they are mood congruent. Psychotic features are considered mood congruent if their content fits in with typical depressive subjects such as guilt, illness, death, poverty or appropriate punishment. It

is unclear whether psychotic depression is merely a severe form of depression, or whether it is in fact a distinct form of depression. According to the DSM-IV, depression with psychotic features is classified as a severe form of depression.

Diagnosing depression with psychotic features has considerable value, because the response rate to antidepressants may be inferior to that of non-psychotic depression. Furthermore, the response rate to ECT in depression with psychotic features is clearly superior compared with depression without psychotic features.

In this thesis we use the definitions as described in the DSM-IV. We have restricted our research to depressed patients meeting the criteria for a major depressive disorder. This means explicitly excluding depressed patients with bipolar disorder since those patients need different treatment when in a depressed episode (Nolen and Bloemkolk, 2000).

Characteristics of depressed inpatients

There is no consensus as to whether or not inpatients show higher total scores on depression rating scales than outpatients, but melancholic features are more common among inpatients (Mendlowicz et al., 1998; Stage et al., 1998). Psychotic features are exceptional among depressed outpatients, while 20-30% of depressed inpatients show psychotic symptoms (Bouvy, 1997). Furthermore, many depressed inpatients show a high degree of treatment resistance and have an index episode that lasts longer than one year (Bouvy, 1997).

All the patients participating in the trials presented in this thesis were admitted to a depression unit. These units are specifically designed for the treatment of patients suffering from severe depressive disorders, with specialized staffing and environment. In an optimal and positive setting, the depression units concentrate on all forms of treatment currently possible which are both clinically appropriate and, as far as possible, evidence based. Part of the program includes measures to structure the course of the day and to activate the patient.

The aim of the studies presented here is to improve the efficacy of treatment, driven by the need to understand the therapeutic process. These studies were conducted under optimal conditions with regard to diagnostic/treatment procedures and clinical follow-up, which was possible due to the specialized nature of the two depression units.

Treatment algorithm

The treatment algorithm under study in this thesis consists of four steps (figure 1).

The first choice in the treatment of a depressive inpatient is usually that between a selective serotonin reuptake inhibitor (SSRI) or a tricyclic antidepressant (TCA).

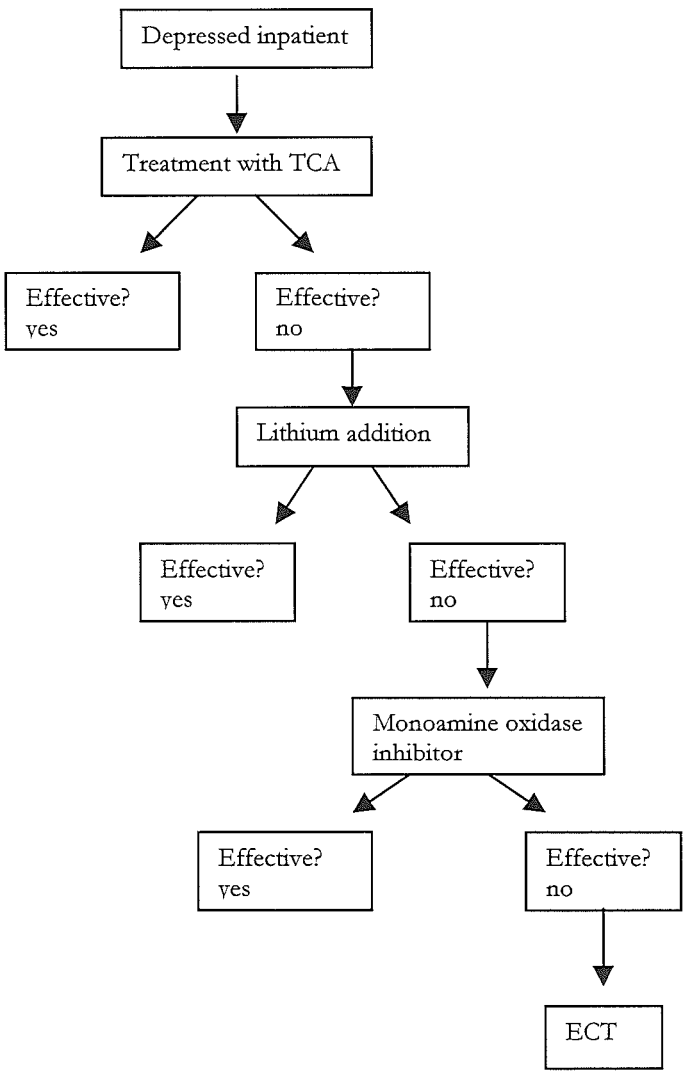


Figure 1. Treatment algorithm for depressed inpatients

Recent studies tended to favor the latter group of antidepressants for the treatment of inpatients (Anderson, 2000; Bruijn et al., 1999); however, it is unclear whether the SSRIs differ from each other in efficacy. In many studies comparing a new antidepressant such as an SSRI with TCAs, the lack of a significant difference in efficacy has been interpreted as a therapeutic equivalency. In the majority of these studies, however, difference in efficacy may have been missed due to a low statistical power or to various other methodological problems. For example, the studies were mainly conducted with outpatients instead of inpatients, drop-out rates were high, co-medication obscuring efficacy was allowed, and the dosing of a TCA was low due to the flexible dose design often used. One of the advantages of the use of TCAs is the possibility to adjust dosage according to plasma level. This offers the advantage of both optimal dosing and treatment compliance. Such dose adjustment according to plasma level might also benefit treatment with SSRIs in depressed inpatients. However, no efficacy studies with dose adjustment to plasma levels for SSRIs have been conducted among inpatients.

The first research question in this thesis concerns the first step of the algorithm. In a trial with inpatients without the above-mentioned methodological shortcomings we would like to address the question whether an SSRI, fluvoxamine, is as effective as a TCA, imipramine. Both drugs will be dose adjusted to plasma levels and we aim to include 150 patients.

Some patients do not respond to the first antidepressant, whether a TCA or an SSRI, the number ranging from 30-65% dependent on the population under study. Treatment strategies in case of refractoriness are of major importance. However, few scientific data are available which allow to make a rational choice between antidepressants (Guscott and Grof, 1991; Nolen and Haffmans, 1989).

In the case of lack of response to the first antidepressant, different strategies can be applied. The addition of lithium is one of the most commonly used and best studied (Austin et al., 1991; Bauer and Dopfmer, 1999). Lithium was found to augment several SSRIs (Baumann et al., 1996; Katona et al., 1995) but no comparison has been made between two treatment strategies with a TCA and an SSRI. In this thesis we compare two treatment strategies whereby lithium is added after non-remission to a TCA, imipramine, and after non-remission to an SSRI, fluvoxamine.

Another alternative for resistant patients is treatment with irreversible monoamine oxidase inhibitors. Tranylcypromine is effective in refractory depression (Nolen et al., 1988) but has only moderate tolerability. Phenelzine has not been

studied in refractory depressed inpatients and might be a promising alternative to tranylcypromine.

The indication for electroconvulsive therapy (ECT) is usually medication-resistant depressive disorder (American Psychiatric Association, 2001). ECT is usually discontinued after its successful use. Although many patients receive ECT after antidepressants have failed, medication is often reinstalled to prevent relapse after successful ECT. Since the use of ECT in medication-resistant depressive patients, the relevance of this earlier research is questionable. Recent research suggests that resistance to antidepressant medication before ECT is related to a high relapse rate after ECT when medication is used for relapse prevention (Sackeim et al., 1990).

In the Netherlands, medication-resistant depression used to be the most common indication for ECT. Since the pretreatment is more rigorous in a Dutch population treated with ECT compared to recent research in the USA, we hypothesized that relapse prevention with imipramine with adequate plasma levels would not differ from placebo in efficacy.

In short, the above-mentioned treatments are the options for depressed inpatients and medication-resistant depressed inpatients. This thesis explores the major topics in the algorithm of the treatment of depressed inpatients. In each phase of the decribed steps, we have studied important topics related to efficacy and tolerability in the treatment of depressed inpatients.

Aims of the study

The aim of the study reported in *Chapter 2* was to compare the efficacy of imipramine with that of fluvoxamine. Previous studies showed that imipramine had good efficacy and moderate tolerability whereas fluvoxamine is considered the most promising serotonin re-uptake inhibitor with regard to efficacy in severely depressed patients (Gatti et al., 1996). Other studies suggest that TCAs (such as imipramine) are more efficacious compared to various SSRIs (DUAG, 1986, 1990), but these trials did not use targeted blood level dosing of the TCAs and SSRIs. Therefore, we compared one of the standard TCAs (imipramine) with one of the oldest SSRIs (fluvoxamine). Both drugs were dosed with targeted blood levels so as to detect differences in efficacy without suboptimal dosing and non-compliance.

Chapter 3 presents a comparison of two treatment strategies: imipramine versus fluvoxamine, both followed by addition of lithium. Lithium addition is a quick and effective strategy that can be applied after non-response to the first drug. This study

compared the effect of lithium addition to both imipramine and fluvoxamine with regard to their efficacy and tolerability in depressed inpatients.

Chapter 4 presents the results of a double-blind study of tranylcypromine versus phenelzine in antidepressant-refractory depressed inpatients. Tranylcypromine, a non-selective inhibitor of monoamine oxidase (MAOI), is the first treatment of choice in depression, refractory to both antidepressants and lithium addition. Tranylcypromine has been shown to have good efficacy but only moderate tolerability. In the search for an MAOI with better tolerability and equal efficacy, we performed this double-blind study to compare tranylcypromine with phenelzine.

Chapters 5 and *6* present the results of double-blind placebo-controlled studies on the effects of the use of alfentanil and esmolol, respectively, during electroconvulsive therapy (ECT). These studies were performed because patients undergoing ECT develop considerable tachycardia and/or hypertension during the seizure. Both drugs were studied with regard to their potential to prevent (alfentanil) or to treat (esmolol) these effects of ECT. Use of these drugs could be of benefit, especially in patients with a high risk of cardiovascular diseases.

Chapter 7 presents a study comparing the short-term efficacy of ECT in depressed patients with delusions with that in non-delusional depressed patients. This study was performed because there is lack of consensus concerning the possible predictive value of specific clinical characteristics, e.g. delusions and melancholic features, with regard to response to ECT.

Chapter 8 presents the results of a naturalistic one-year follow-up study after successful ECT and the influence of illness characteristics on relapse. This study was conducted to explore the discrepancy between disappointing results of follow-up studies from the USA and a more favorable clinical impression concerning post-ECT relapse in the Netherlands.

Chapter 9 reports on a double-blind study comparing imipramine with placebo in the prevention of relapse 6 months following successful ECT. Again, results from follow-up studies from the USA suggested that continuation treatment with antidepressants after successful ECT failed to prevent relapse with antidepressant-resistant depressed patients (Prudic et al., 1990; Prudic et al., 1996). Because in the Netherlands ECT is an exceptional treatment applied mainly to antidepressant-resistant depressed inpatients, it was considered necessary to perform this study.

Chapter 10 presents a general discussion of the overall results and implications for future studies.

References

American Psychiatric Association (2001). *The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training and Privileging* (2nd ed). Washington, DC: American Psychiatric Association Committee on Electroconvulsive Therapy.

Amore M, Bellini M, Berardi D, Berlinzani L, Cervino G, Cremonini A, Ferrari G, Innamorati A. (1989). Double-blind comparison of fluvoxamine and imipramine in depressed patients. *Current Therapeutic Research,* 46:815-820.

Anderson IM. (2000). Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. *Journal of Affective Disordorders,* 58:19-36.

Anderson IM, Nutt DJ, Deakin JF (2000). Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 1993 British Association for Psychopharmacology guidelines. British Association for Psychopharmacology. *Journal of Psychopharmacology,* 14:3-20.

Angst J (1993). Severity of depression and benzodiazepine co-medication in relationship to efficacy of antidepressants in acute trials. *Human Psychopharmacology* 8:401-407.

Austin MP, Souza FG, Goodwin GM (1991). Lithium augmentation in antidepressant-resistant patients. A quantitative analysis. *British Journal of Psychiatry* 159:510-514.

Bauer M, Dopfmer S (1999). Lithium augmentation in treatment-resistant depression: meta-analysis of placebo-controlled studies. *Journal of Clinical Psychopharmacology* 19:427-434.

Baumann P, Nil R, Souche A, Montaldi S, Baettig D, Lambert S, Uehlinger C, Kasas A, Amey M, Jonzier-Perey M (1996). A double-blind, placebo-controlled study of citalopram with and without lithium in the treatment of therapy-resistant depressive patients: a clinical, pharmacokinetic, and pharmacogenetic investigation. *Journal of Clinical Psychopharmacology* 16:307-314.

Benkert O, Szegedi A, Wetzel H (1996). Minimum effective dose for antidepressants - an obligatory requirement for antidepressant drug evaluation? *International Clinical Psychopharmacology* 11:177-185.

Bijl RV, Van Zessen G, Ravelli A (1997). Psychiatric morbidity among adults in The Netherlands: the NEMESIS-Study. II. Prevalence of psychiatric disorders. Netherlands Mental Health Survey and Incidence Study. *Nederlands Tijdschrift voor Geneeskunde* 141:2453-2460.

Bollini P, Pampallona S, Tibaldi G, Kupelnick B, Munizza C (1999). Effectiveness of antidepressants. Meta-analysis of dose-effect relationships in randomised clinical trials. *British Journal of Psychiatry* 174:297-303.

Bouvy P (1997). *Behandeling van opgenomen depressieve patienten met klassieke antidepressiva.* PhD thesis, Nijmegen.

Bruijn JA, Moleman P, Mulder PG, Van den Broek WW (1999). Depressed in-patients respond differently to imipramine and mirtazapine. *Pharmacopsychiatry,* 32:87-92.

Bruijn JA, Moleman P, Mulder,PG, Van den Broek WW, Van Hulst AM, Van der Mast RC, Van de Wetering BJM (1996). A double-blind, fixed blood-level study comparing mirtazapine with imipramine in depressed in-patients. *Psychopharmacology* 127:231-237.

Claghorn JL, Earl CQ, Walczak DD, Stoner KA, Wong LF, Kanter D, Houser VP (1996). Fluvoxamine maleate in the treatment of depression: a single-center, double-blind, placebo-controlled comparison with imipramine in outpatients. *Journal of Psychopharmacology* 16:113-120.

Dominguez RA, Goldstein BJ, Jacobson AF, Steinbook RM (1985). A double-blind placebo-controlled study of fluvoxamine and imipramine in depression. *Journal of Clinical Psychiatry* 46:84-87.

DUAG (1986). Citalopram: clinical effect profile in comparison with clomipramine. A controlled multicenter study. Danish University Antidepressant Group. *Psychopharmacology* 90:131-138.

DUAG (1990). Paroxetine: a selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. Danish University Antidepressant Group. *Journal of Affective Disorders* 18:289-299.

Fabre L, Birkhimer LJ, Zaborny BA, Wong LF, Kapik BM (1996). Fluvoxamine versus imipramine and placebo: a double-blind comparison in depressed patients. *International Clinical Psychopharmacology* 11:119-127.

Feighner JP, Boyer WF, Meredith CH, Hendrickson GG (1989). A placebo-controlled inpatient comparison of fluvoxamine maleate and imipramine in major depression. *International Clinical Psychopharmacology* 4:239-244.

Foglia JP, Perel JM, Nathan RS, Pollock BG, Lin FC, Nerayanan S (1990). Therapeutic Drug Monitoring (TDM) of fluvoxamine, a selective antidepressant. *Clinical Chemistry* 36:1043.

Gatti F, Bellini L, Gasperini M, Perez J, Zanardi R., Smeraldi E (1996). Fluvoxamine alone in the treatment of delusional depression. *American Journal of Psychiatry* 153:414-416.

Glassman AH, Perel JM, Shostak M, Kantor SJ, Fleiss JL (1977). Clinical implications of imipramine plasma levels for depressive illness. *Archives of General Psychiatry* 34:197-204.

Guelfi JD, Dreyfus JF, Pichot P (1983). A double-blind controlled clinical trial comparing fluvoxamine with imipramine. *British Journal of Clinical Pharmacology,* 15 (Suppl 3*)*:411S-417S.

Guscott R., Grof P (1991). The clinical meaning of refractory depression: a review for the clinician. *American Journal of Psychiatry* 148:695-704.

Guy W. (1976). *Assessment manual for psychopharmacology.* Rochville: U.S. Department of Healthy Education and Welfare.

Guy W, Wilson WH, Ban TA, King DL, Manov G, Fjetland OK (1984). A double-blind clinical trial of fluvoxamine and imipramine in patients with primary depression. *Psychopharmacolgy Bulletin* 20:73-78.

Hamilton M (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry* 23:56-61.

Hartter S, Wetzel H, Hammes E, Torkzadeh M, Hiemke C (1998). Nonlinear pharmacokinetics of fluvoxamine and gender differences. *Therapeutic Drug Monitor* 20:446-449.

Hirschfeld RM (1999). Efficacy of SSRIs and newer antidepressants in severe depression: comparison with TCAs. *Journal of Clinical Psychiatry* 60:326-335.

Itil TM, Shrivastava RK, Mukherjee S, Coleman BS, Michael ST (1983). A double-blind placebo-controlled study of fluvoxamine and imipramine in out-patients with primary depression. *British Journal of Clinical Pharmacology* 15 (Suppl 3):433S-438S.

Kasper S, Moller HJ, Montgomery SA, Zondag E (1995). Antidepressant efficacy in relation to item analysis and severity of depression: a placebo-controlled trial of fluvoxamine versus imipramine. *International Clinical Psychopharmacoly* 9 (Suppl 4):3-12.

Katona CL, Abou-Saleh MT, Harrison DA, Nairac BA, Edwards DR., Lock T, Burns RA, Robertson MM (1995). Placebo-controlled trial of lithium augmentation of fluoxetine and lofepramine. *British Journal of Psychiatry* 166:80-86.

Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Archives of General Psychiatry* 51:8-19.

Lapierre YD, Browne M, Horn E, Oyewumi LK, Sarantidis D, Roberts N, Badoe K, Tessier P (1987). Treatment of major affective disorder with fluvoxamine. *Journal of Clinical Psychiatry* 48:65-68.

Lingam R, Scott J (2002). Treatment non-adherence in affective disorders. *Acta Psychiatrica Scandinavica* 105:164-172.

Lydiard RB, Laird LK, Morton WA Jr, Steele TE, Kellner C, Laraia MT, Ballenger JC (1989). Fluvoxamine, imipramine, and placebo in the treatment of depressed outpatients: effects on depression. *Psychopharmacoly Bulletin* 25:68-70.

March JS, Kobak KA, Jefferson JW, Mazza J, Greist JH (1990). A double-blind, placebo-controlled trial of fluvoxamine versus imipramine in outpatients with major depression. *Journal of Clinical Psychiatry* 51:200-202.

Mendlowicz MV, Rapaport MH, Thompson P, Kelsoe JR., Golshan S, Judd LL, Gillin, JC (1998). A comparison of descriptive characteristics of male outpatients and inpatients with affective disorders. *International Clinical Psychopharmacology* 13:245-252.

Nair NP, Bakish D, Saxena B, Amin M, Schwartz G, West TE (1996). Comparison of fluvoxamine, imipramine, and placebo in the treatment of outpatients with panic disorder. *Anxiety* 2:192-198.

Niklson IA, Reimitz PE, Sennef C (1997). Factors that influence the outcome of placebo-controlled antidepressant clinical trials. *Psychopharmacoly Bulletin* 33:41-51.

Nolen WA, Bloemkolk D (2000). Treatment of bipolar depression, a review of the literature and a suggestion for an algorithm. *Neuropsychobiology* 42 (Suppl 1):11-17.

Nolen WA, Haffmans J (1989). Treatment of resistant depression. Review on the efficacy of various biological treatments, specifically in major depression resistant to cyclic antidepressants. *International Clinical Psychopharmacoly* 4:217-228.

Nolen WA, Van de Putte JJ, Dijken WA, Kamp JS, Blansjaar BA, Kramer HJ, Haffmans J (1988). Treatment strategy in depression. II. MAO inhibitors in depression resistant to cyclic antidepressants: two controlled crossover studies with tranylcypromine versus L-5-hydroxytryptophan and nomifensine. *Acta Psychiatrica Scandinavica* 78:676-683.

Norton KR, Sireling LI, Bhat AV, Rao B, Paykel ES (1984). A double-blind comparison of fluvoxamine, imipramine and placebo in depressed patients. *Journal of Affective Disorders* 7:297-308.

Ormel J, Sytema S (1999). Epidemiologische aspecten van stemmingsstoornissen. In Den Boer J and Ormel J (eds), *Handboek Stemmingsstoornissen.* Maarssen: Elsevier/De Tijdstroom.

Perry PJ (1996). Pharmacotherapy for major depression with melancholic features: relative efficacy of tricyclic versus selective serotonin reuptake inhibitor antidepressants. *Journal of Affective Disorders* 39:1-6.

Peselow ED, Sanfilipo MP, Difiglia C, Fieve RR (1992). Melancholic/endogenous depression and response to somatic treatment and placebo. *American Journal of Psychiatry* 149:1324-1334.

Potter WZ, Rudorfer MV, Manji H (1991). The pharmacologic treatment of depression. *New England Journal of Medicine* 325:633-642.

Prudic J, Haskett RF, Mulsant B, Malone KM, Pettinati HM, Stephens S, Greenberg R, Rifas SL, Sackeim HA. (1996). Resistance to antidepressant medications and short-term clinical response to ECT. *American Journal of Psychiatry* 153:985-992.

Prudic J, Sackeim H, Devanand D (1990). Medication resistance and clinical response to electroconvulsive therapy. *Psychiatry Research* 31:287-296.

Regier DA, Narrow WE, Rae DS, Manderscheid RW, Locke BZ, Goodwin FK (1993). The de facto US mental and addictive disorders service system. Epidemiologic catchment area prospective 1-year prevalence rates of disorders and services. *Archives of General Psychiatry* 50:85-94.

Roose SP, Glassman AH, Attia E, Woodring S (1994). Comparative efficacy of selective serotonin reuptake inhibitors and tricyclics in the treatment of melancholia. *American Journal of Psychiatry* 151:1735-1739.

Sackeim HA, Prudic J, Devanand DP, Decina P, Kerr B, Malitz S (1990). The impact of medication resistance and continuation pharmacotherapy on relapse following response to electroconvulsive therapy in major depression. *Journal of Clinical Psychopharmacolgy* 10:96-104.

Spigset O, Martensson B (1999). Fortnightly review: drug treatment of depression. *British Medical Journal* 318:1188-1191.

Spitzer R, Endicot J (1978). *Schedule for Affective Disorders and Schizofrenia (SADS)* (3rd ed.). New York: Biometric Research, New York State Psychiatric Institute.

Stage KB, Bech P, Gram LF, Kragh-Sorensen P, Rosenberg C, Ohrberg S (1998). Are in-patient depressives more often of the melancholic subtype? Danish University Antidepressant Group. *Acta Psychiatrica Scandinavica* 98:432-436.

2 | A double-blind study comparing imipramine with fluvoxamine in depressed inpatients.

In press: Psychopharmacology, 2004

Walter W. van den Broek
Tom K. Birkenhäger
Paul G.H. Mulder
Jan A. Bruijn
Peter Moleman

Chapter 2.

A double-blind study comparing imipramine with fluvoxamine in depressed inpatients.

Walter W. van den Broek, Tom K. Birkenhäger, Paul G.H. Mulder, Jan A. Bruijn, Peter Moleman

Abstract

Objective:

To compare the efficacy of imipramine and fluvoxamine in inpatients from two centers suffering from a depressive disorder according to DSM IV criteria.

Methods:

The study included 141 patients with a depressive disorder according to DSM IV criteria. After a drug-free and placebo run-in period of one week, patients were randomized to imipramine or fluvoxamine; doses of both drugs were adjusted to a predefined target blood level. Efficacy was evaluated four weeks after attaining predefined adequate plasma level.

Results:

The mean age of the study group (47 males, 94 females) was 51.8 (range 19-65) years. Of these 141 patients, 56 had episode duration longer than one year, 48 had mood congruent psychotic features, and 138 patients received medication. Seven patients did not complete the medication trial. The total number of patients using concurrent medication was 12/138 (8.6%).

On the primary outcome criteria patients on imipramine improved significantly better on the change of illness severity score of the CGI (χ^2exact trend test=4.089, df=1, p=0.048). There was no significant difference in 50% or more reduction on the HRSD, the other primary outcome criterion.

On the secondary outcome criteria the mean reduction of the HRSD scores was significantly larger in the imipramine group than in the fluvoxamine group (mean difference=3.1, Standard Error (SE) =1.4, t=2.15, df=136, p=0.033). There was no significant difference in the number of patients with an HRSD $\leq$ 7 at the final evaluation.

Conclusions:

In depressed inpatients imipramine is more efficacious than fluvoxamine. Both drugs were well tolerated by all patients.

Keywords

Imipramine, fluvoxamine, concentration targeted trial, depressive disorder, inpatients, major depression.

Introduction

Meta analyses have shown that tricyclic antidepressants (TCAs) have superior efficacy to selective serotonin reuptake inhibitors (SSRIs) in depressed inpatients (Anderson, 2000), but no superiority was shown for imipramine separately. Considering the SSRIs separately, there was no significant advantage for the TCAs over fluvoxamine. In depressed outpatients imipramine and fluvoxamine have shown comparable efficacy (Claghorn et al., 1996; Fabre et al. 1996). In one study, fluvoxamine was significantly superior to placebo in severely depressed patients as shown by improvements in the score on the 17-item Hamilton Rating Scale for Depression (HRSD) and Clinical Global Improvement (CGI) scores; the subjects in that study were mostly outpatients (Kasper et al., 1995). In two placebo-controlled trials with inpatients, fluvoxamine was significantly superior to placebo (Feighner et al., 1989; Lapierre et al., 1987). In these two latter studies and in three studies without placebo control (also with inpatients) no significant differences in efficacy between imipramine and fluvoxamine were observed (Amore et al., 1989; Guelfi et al., 1983; Guy et al., 1984).

We have previously shown that imipramine is considerably more effective than mirtazapine in inpatients, in contrast to other studies comparing mirtazapine with TCAs (Bruijn et al., 1996). Possible explanations for the differences between this earlier study and other studies are: optimalisation of doses with blood level targeting, the paucity of concurrent medication, high compliance and the low drop-out rate (Bruijn et al., 1996).

In the present study, using similar methods and in a similar patient population, we compared the efficacy of imipramine and an SSRI, fluvoxamine.

Materials and methods

The study was preformed in two centers, at the department of Psychiatry of the Erasmus Medical Centre in Rotterdam (EMCR) and at the Parnassia Psychomedical Centre (PPC) in The Hague. Both units have a regional function for treatment of uncomplicated depressed patients and a super-regional function for treatment of therapy-resistant depressed patients. Patients were enrolled in the study from April 1997 to July 2001. After giving written informed consent, placebo was administered single blind during 4 days. At the end of this period patients were again assessed on the 17-item version of the HRSD (Hamilton, 1960) and those still meeting inclusion criteria were randomly allocated to a double-blind treatment with either imipramine or fluvoxamine. A score of 17 or higher on the HRSD was the inclusion criterion.

Doses of both drugs were adjusted to obtain predefined blood levels. Patients were rated weekly for depression severity with the HRSD and CGI scale (Guy, 1976). Outcome was assessed 4 weeks after attaining these predefined blood levels. Concurrent medication was not allowed except for 1-6 tablets a day containing 45 mg of an extract of valerian in case of severe anxiety or insomnia; this extract was assumed to be without antidepressant effect. According to the protocol in exceptional cases lorazepam, 1-3 mg a day for intolerable anxiety, or haloperidol, 1-10 mg a day in case of intolerable psychotic symptoms, respectively, was allowed. The degree of pre-treatment during the current episode was evaluated using the Antidepressant Treatment History Form (ATHF) (Prudic et al., 1996; Sackeim et al., 1990). A research nurse systematically assessed side-effects.

Patient selection

All psychotropic drugs were discontinued after admission. Patients were screened for inclusion and exclusion criteria before the initial placebo period. The HRSD was administered before and again at the end of the placebo period. Eligible patients had to be drug-free for at least 3 days before baseline assessment.

Included were patients aged 18-65 years who had a DSM IV diagnosis of depressive disorder and an HRSD score $\geq$ 17. The diagnosis was assessed with the depression part of the Schedule for Affective Disorders and Schizophrenia (Spitzer and Endicot, 1978). The three research psychiatrists (WvdB, JB in EMCR and TB in PCC) did all assessments. During the trial, interrater sessions with the investigating psychiatrists took place 6 times a year. The sum of all HDRS items of the three research psychiatrists was used to test interrater reliability (kappa=0.95).

Excluded were patients with schizophrenia, bipolar or schizo-affective disorder, organic brain syndrome, chronic alcohol or drug abuse, relevant somatic illness, and presence of absolute contraindication for either imipramine or fluvoxamine, refractoriness to clinical treatment with a TCA or fluvoxamine with adequate plasma level for at least 4 weeks during present episode, pregnancy or the risk to become pregnant, and an improvement of $\geq$ 50% on the HRSD during the 4-day placebo run-in period.

Study medication

Tablets identical in appearance, weight and taste containing either imipramine or fluvoxamine were administered once a day at 10 p.m., starting with 75 mg. Preparation of the tablets was done by the pharmacist and the randomization was done using a computer generated randomization list with randomly permuted blocks of random block size. After two days, the dose was doubled unless severe side-effects were observed. The pharmaceutical laboratory of the EMCR monitored blood levels once a week. The hospital pharmacist advised on the adjustment of the dosage, based on the targeted blood level according to a predefined dosage table. This was communicated to the treating physician in percentages in order to prevent unblinding. The treating physicians were not involved in the ratings of this study.

The predefined blood level for imipramine + desimipramine was 200-300 ng/ml (100% equals 250 ng/ml) and for fluvoxamine 150-200 ng/ml (100% equals 175 ng/ml).

Data analysis and statistical methods

From previous research the assumption for a power analysis was that 50% of patients would respond to imipramine (Bruijn et al., 1996). A difference of 20% in response would be clinically relevant. With an α of 0.05 and a β of 0.20 (power 80%) it was planned to include two groups of 83 patients.

The a priori principal end point of the trial was 4 weeks after attaining adequate plasma levels.

The following primary response criteria were analyzed; a 50% reduction or more of the HRSD score and improvement according to the CGI after 4 weeks of an adequate predefined blood level. The secondary outcome criteria were a HRSD score of $\leq$ 7, and the mean reduction in HRSD scores. Change from baseline of the CGI as categorical ordinal variable was compared between the two treatments using a χ^2

exact trend test and the last observation carried forward. The *t*-test was used to compare continuous outcome variables with a Gaussian-shaped distribution. Changes from baseline of the last observed HRSD score were compared between the two treatments groups using analysis of covariance (ANCOVA) with the baseline HRSD score as covariate.

For the two response criteria defined as a 50% decrease of the HRSD and a score of ≤ 7 on the HRSD we analyzed the difference in time to response between the two treatment groups. Duration of treatment until meeting the response criterion was the survival time variable in a Cox proportional hazards model. Drop-outs were censored at the time of drop-out. Analyses for testing differences in response between the two treatments were adjusted for the following prespecified co-variables: duration of current episode, psychotic features, and previous treatment during current episode. Adjustment for center was made by stratification. Statistical significance was defined as $p< 0.05$.

Ethical considerations

The protocol was approved by the Ethics Committee of the Erasmus Medical Centre Rotterdam. The protocol was carried out in accordance with the ethical standards laid down in the declaration of Helsinki.

Results

Of the 201 patients with a depressive disorder at the first center (EMCR), 94 (47%) fulfilled one or more exclusion criteria, 28 (14%) patients refused participation, and 79 (39%) patients participated. In the second centre (PPC) 145 patients were diagnosed with a depressive disorder, of which 78 (54%) fulfilled one or more exclusion criteria, 5 (3%) refused participation and 62 (43%) patients participated (Figure 1).

A total of 141 patients (47 male, 94 female) gave informed consent, 79 in the first center (EMCR), 62 in the second center (PPC). From the 141 eligible patients 55 patients were pretreated with an SSRI and 32 with a TCA but none as inpatient with adequate plasma level for at least 4 weeks during the present episode.

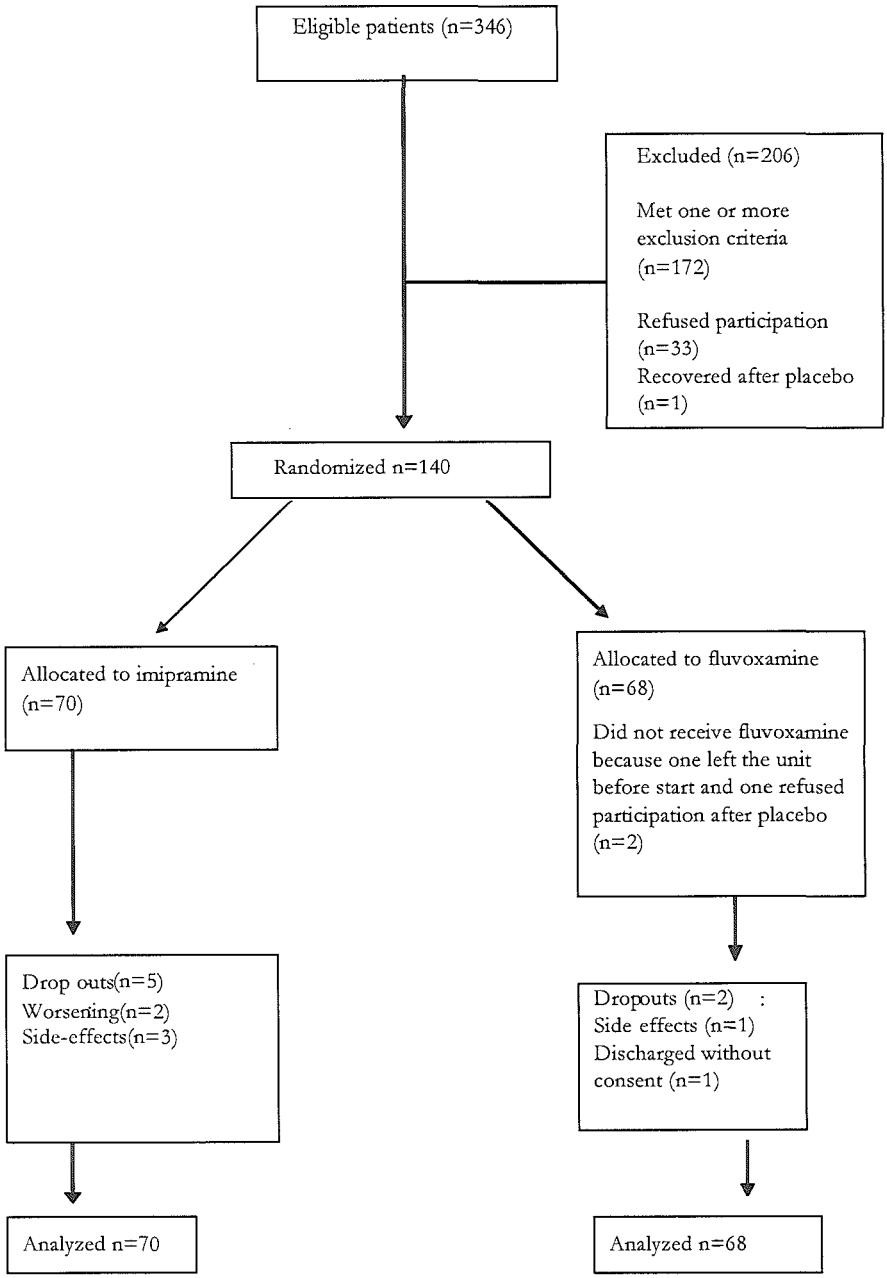


Figure 1. Flow diagram showing the phases of the randomized trial

Three patients were excluded from analysis: one patient recovered after the placebo period and two patients were randomized but never received medication (one left the unit before the start of the trial, the other refused participation after the placebo period). Thus 138 patients started the medication, either imipramine (n=70) or fluvoxamine (n=68) (Table 1). Seven patients dropped-out during the trial (Table 2).

Table 1. Characteristics of the patients randomized in the trial.

	Imipramine (n=70)	Fluvoxamine (n=68)
Age: mean ± SD (range) in years	51± 9.1 (19-65)	53±9.9 (27-65)
Sex: male/female	27/43	19/51
Duration current episode		
< 1 year	46 (66%)	36 (53%)
> 1 year	24 (34%)	32 (47%)
First episode	42 (60%)	34 (50%)
Psychotic type	25 (36%)	23 (34%)
Married	43/70 (61%)	44/68 (65%)
Education:		
Less than High School	10/70 (14%)	12/68 (18%)
Living alone	22/70 (31%)	18/68 (26%)

Table 2. Reason for drop-out during the trial

Reason for drop-out	Imipramine (n=70)	Fluvoxamine (n=68)
Side-effects	3 (4%)	1 (1%)
Worsening	2 (3%)	
Discharge without consent		1 (1%)
Total	5 (7%)	2 (2%)

Blood levels and doses

The mean time to reach the predefined blood levels was 13.3 (SD±4.4, range 5-21) days for imipramine and 12.6 (SD±6.2, range 4-33) days for fluvoxamine, a non-significant difference (Mann-Whitney test). The mean daily dose during the 4 weeks on the predefined blood level for imipramine was 253.3 (SD±76.9, range 150-450) mg/day with a mean blood level of 290.8 ng/ml (SD±68.50, range 191.86-520.60) and for fluvoxamine 287.5 (SD±265.8, range 150-1800) mg/day with a mean blood level of 215.0 (SD±39.98, range 108.6-325.0) ng/ml, respectively. The distribution of doses needed to obtain the predefined blood level with fluvoxamine was skewed with an outlier of 1800 mg. The skewed distribution is in line with the non-linear kinetics of fluvoxamine (Hartter e.a., 1998).

Concomitant medication

Four patients on imipramine (4/70) and five patients on fluvoxamine (5/68) were prescribed lorazepam because of intolerable anxiety. One patient on imipramine (1/70) and two patients on fluvoxamine (2/68) were treated with an antipsychotic. The total number of patients using concurrent medication was 12/138 (8.6%), which was ignored in the analysis because of the small number of patients.

Treatment effects

All outcome criteria were assessed after 4 weeks of attaining an adequate predefined blood level.

According to the primary outcome criterion of a 50% reduction or more on the HRSD, 36 of 70 (51%) patients on imipramine were responders compared to 23 of 68 (34%) patients on fluvoxamine. The average follow-up time for imipramine was 4.6 weeks and for fluvoxamine 5.1 weeks. There was no significant difference in time to response using the Cox proportional hazards model, stratified for center and adjusted for duration of the current episode (longer or shorter than one year), psychotic features and adequate previous treatment during the current episode. The response rate ratios of fluvoxamine relative to imipramine for 50% reduction on the HRSD was: 0.66 (CI: 0.39-1.12, p=0.12). The degree of pre-treatment during the current episode was evaluated using the Antidepressant Treatment History Form (ATHF) (Prudic et al., 1996; Sackeim et al., 1990). Psychotic features did not significantly alter the response to treatment.

There was a significant difference on the other primary outcome criterion between imipramine and fluvoxamine on the change of illness severity score of the CGI, patients on imipramine improved significantly better (χ^2 exact trend test=4.089, df=1, p=0.048) (Figure 2).

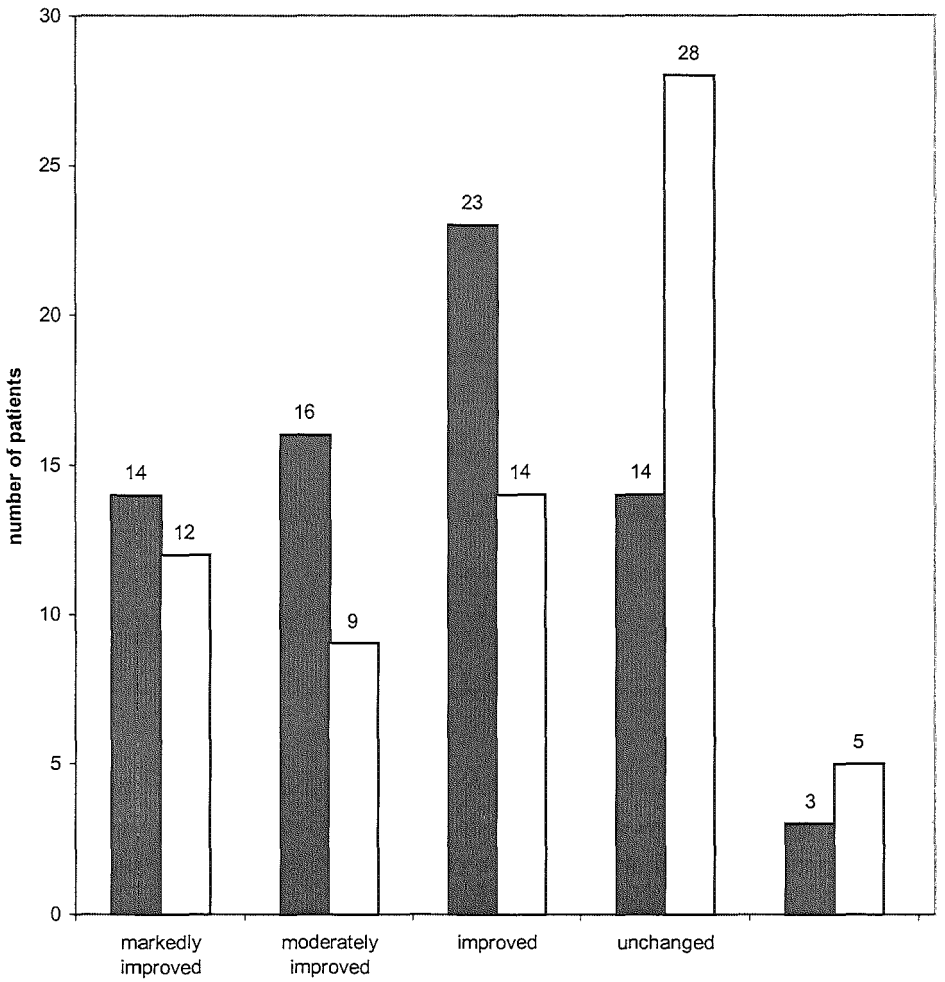


Figure 2. Clinical Global Improvement scores compared to baseline after 4 weeks of an adequate predefined blood level.

The secondary outcome criterion complete remission (HRSD score of ≤ 7) was achieved by 20/70 (28.6%) patients on imipramine and 12/68 (17.6%) patients on fluvoxamine. The follow-up for imipramine was an average of 5.1 weeks, for fluvoxamine 5.6 weeks. There was no significant difference in time to response using the Cox proportional hazards model, stratified by center and adjusted for duration of the current episode (longer or shorter than one year), psychotic features and adequate previous treatment during the current episode. The response rate ratios for fluvoxamine relative to imipramine for an HRSD score ≤7 was: 0.64 (CI: 0.31-1.32, p=0.22).

The other secondary outcome criterion, the mean reduction of the HRSD adjusted for baseline was significantly lower in the imipramine group than in the fluvoxamine group (mean difference=3.0, Confidence Interval (CI) = 0.245 to 5.81, t=2.15, df=135, p=0.033) (Table 3).

Table 3. Mean HRSD scores at baseline (n=138) and at the last visit after 4 weeks of an adequate predefined blood level.

	Imipramine (n=70)	Fluvoxamine (n=68)
Baseline HRSD ± SD	24.5 ± 5.3	24.4 ± 4.9
Endpoint HRSD ±SD	15.1 ± 8.5	18.1 ± 9.2

HRSD= Hamilton Rating Scale of Depression, SD= Standard Deviation

Discussion

The aim of the present study was to compare imipramine and fluvoxamine in depressed inpatients with adjustment of the dosage to a target blood level. In contrast to earlier studies we found a significant difference in response in favor of imipramine compared to fluvoxamine (Ware, 1997).

Our results are different from previous studies comparing imipramine with fluvoxamine in outpatients (Dominguez et al., 1985; Itil et al., 1983; Lydiard et al., 1989; March et al., 1990; Nair et al., 1996; Norton et al., 1984) and inpatients (Amore et al., 1989; Feighner et al., 1989; Guelfi et al., 1983; Guy et al., 1984; Lapierre et al., 1987). These studies did not find a significant difference in efficacy.

On the other hand, the present study is in agreement with the DUAG studies (DUAG, 1986, 1990) and the study of Roose et al. (Roose et al., 1994). These studies reported that TCAs are more effective than SSRIs in depressed inpatients.

We previously reported an even larger difference in the HRSD score of 5.1 points (Standard error= 1.8, t=2.83, df=95, p=0.006) between imipramine and mirtazapine in a study with comparable methodology (Bruijn et al., 1996), also different from most other studies comparing mirtazapine with TCAs. This reinforces our arguments as to the origin of these differences.

Inclusion criteria, i.e. a depressive disorder according to DSM IV, are similar in all studies. However, the characteristics of the patients included show some important differences. In the present study, only hospitalized patients were included, in contrast to the majority of the other studies. In addition, patients with psychotic features were not excluded in the present study. Most other studies on inpatients only, had smaller sample sizes which may have led to insufficient power to detect differences (Amore et al., 1989; Feighner et al., 1989; Guy et al., 1984; Lapierre et al., 1987). One study with a large sample size (n= 158) reported a high drop-out rate (Guelfi et al., 1983). In one study psychotic depressed patients were excluded (Amore et al., 1989) and in another study pretreated depressed patients were excluded (Lapierre et al., 1987). We therefore conclude that the patient populations in our studies differ in being exclusively inpatients with severe symptomatology including psychotic features. The low overall response rate may be related to the severity and possibly other distinguishing characteristics of the present patient population. This is in contrast with other publications on the efficacy of SSRIs in severe depression (Hirschfeld, 1999; Zohar et al., 2003).

Establishing the optimum dose of an antidepressant is a problem in practice (Spigset and Martensson, 1999), as well as in clinical trials (Benkert et al., 1996), because many of the possible disturbing side-effects of TCAs occur at sub-therapeutic doses. Flexible dosing, as used in previous studies, leads to the risk of under-dosing of the TCA (Bollini et al., 1999). Thus, the mean dose of imipramine is considerably lower in these studies compared to the present one. Three trials with inpatients reported the mean daily dosage for imipramine and fluvoxamine. The imipramine doses were 112 mg (n=81), 172 mg (n=21) and 159 mg (n=36), respectively (Feighner et al., 1989; Guelfi et al., 1983; Lapierre et al., 1987) compared to 253.3 mg in the present study. The fluvoxamine doses were 221 mg (n=77), 180 mg (n=22) and 145 mg (n=31), respectively compared to 287.5 mg in the present study. According to the revised treatment guidelines of the British Association for Pharmacology (Anderson et al., 2000) doses of 125-150 mg of TCAs are more

effective than lower doses and this advantage appears to increase with severity of depression. In the present study, none of the patients received a dose of imipramine less than 150 mg, while in all comparative studies around 50% of the patients received less effective doses, i.e. below 150 mg. Similarly, a plasma level effect relationship for imipramine has been shown (Glassman et al., 1977). Moreover, monitoring of plasma levels strongly reduces non-compliance (Lingam and Scott, 2002). There is also some evidence for a plasma level effect relationship with fluvoxamine (Walczak et al., 1996), a maximum response with fluvoxamine being found in the range of 160-220 ng/l (Foglia et al., 1990). Since this is close to the range targeted in the present trial, it is unlikely that the choice of target concentration for fluvoxamine was too low. Our mean dose of fluvoxamine was 287.5 mg per day, which is higher than in other trials (Feighner et al., 1989; Guelfi et al., 1983; Lapierre et al., 1987). We, therefore, conclude that the observed difference in efficacy in favor of imipramine is due to optimal dosing.

Only a minority of our patients was treated with benzodiazepines, which is exceptional for comparative trials of antidepressants, especially in inpatients. Less than 10% of the patients participating in our study used any concurrent medication, compared to 55-90% in other studies (Amore et al., 1989; Guelfi et al., 1983; Guy et al., 1984; Lapierre et al., 1987). Use of a benzodiazepine can decrease the power to find differences between comparative drugs (Angst, 1993).

A low drop-out rate appears to contribute to the discriminative power in trials comparing antidepressants (Niklson et al., 1997). Our drop-out rate was 5%, which is less than that reported in other studies (17-50%) (Amore et al., 1989; Feighner et al., 1989; Guelfi et al., 1983; Guy et al., 1984; Lapierre et al., 1987).

In conclusion, the results of this study show a significant difference in efficacy of 3 points on the HRSD between imipramine and the SSRI fluvoxamine, the difference being less than between imipramine and mirtazapine in a previous trial (Bruijn et al., 1996).

This study, in combination with our previous results, indicates that differences in efficacy in favor of a TCA in severely depressed inpatients compared to newer antidepressants (including SSRIs) can be observed in a single trial. Optimal dosing with the use of target concentrations, exclusion of non-compliance, minimal concurrent psychopharmacological medication, and a low drop out rate may each or all be instrumental in this discriminative power. The results appear to prove the superiority of imipramine for the treatment of severely depressed inpatients.

Acknowledgments

This study was supported by an unconditional grant from Solvay Pharma, The Netherlands, the manufacturer of fluvoxamine. We also thank the pharmacy department of the Erasmus MC for the preparation of the medication and the determination of the plasma levels and assistance in dosing the antidepressants.

References

American Psychiatric Association (2001). *The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training and Privileging* (2nd ed). Washington, DC: American Psychiatric Association Committee on Electroconvulsive Therapy.

Amore M, Bellini M, Berardi D, Berlinzani L, Cervino G, Cremonini A, Ferrari G, Innamorati A (1989). Double-blind comparison of fluvoxamine and imipramine in depressed patients. *Current Therapeutic Research* 46:815-820.

Anderson IM (2000). Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. *Journal of Affective Disorders* 58:19-36.

Anderson IM, Nutt DJ, Deakin JF (2000). Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 1993 British Association for Psychopharmacology guidelines. British Association for Psychopharmacology. *Journal of Psychopharmacology* 14:3-20.

Angst J (1993). Severity of depression and benzodiazepine co-medication in relationship to efficacy of antidepressants in acute trials. *Human Psychopharmacology* 8:401-407.

Bollini P, Pampallona S, Tibaldi G, Kupelnick B, Munizza C (1999). Effectiveness of antidepressants. Meta-analysis of dose-effect relationships in randomised clinical trials. *British Journal of Psychiatry* 17:297-303.

Bruijn JA, Moleman P, Mulder PG, Van den Broek WW (1999). Depressed in-patients respond differently to imipramine and mirtazapine. *Pharmacopsychiatry,* 32:87-92.

Bruijn JA, Moleman P, Mulder PG, Van den Broek WW, Van Hulst AM, Van der Mast RC, Van de Wetering BJ (1996). A double-blind, fixed blood-level study comparing mirtazapine with imipramine in depressed in-patients. *Psychopharmacology* 127:231-237.

Claghorn JL, Earl CQ, Walczak DD, Stoner KA., Wong LF, Kanter D, Houser VP (1996). Fluvoxamine maleate in the treatment of depression: a single-center, double-blind, placebo-controlled comparison with imipramine in outpatients. *J Clinical Psychopharmacology* 16:113-120.

Dominguez RA, Goldstein BJ, Jacobson AF, Steinbook RM. (1985). A double-blind placebo-controlled study of fluvoxamine and imipramine in depression. *Journal of Clinical Psychiatry* 46:84-87.

DUAG (1986). Citalopram: clinical effect profile in comparison with clomipramine. A controlled multicenter study. Danish University Antidepressant Group. *Psychopharmacology* 90:131-138.

DUAG (1990). Paroxetine: a selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. Danish University Antidepressant Group. *Journal of Affective Disorders* 18:289-299.

Fabre L, Birkhimer LJ, Zaborny BA, Wong, LF, Kapik BM (1996). Fluvoxamine versus imipramine and placebo: a double-blind comparison in depressed patients. *International Clinical Psychopharmacology* 11:119-127.

Feighner JP, Boyer WF, Meredith CH, Hendrickson GG (1989). A placebo-controlled inpatient comparison of fluvoxamine maleate and imipramine in major depression. *International Clinical Psychopharmacology* 4:239-244.

Foglia JP, Perel JM, Nathan RS, Pollock BG, Lin FC, Nerayanan S (1990). Therapeutic Drug Monitoring (TDM) of fluvoxamine, a selective antidepressant. *Clinical Chemistry* 36:1043.

Gatti F, Bellini L, Gasperini M, Perez J, Zanardi R, Smeraldi E (1996). Fluvoxamine alone in the treatment of delusional depression. *American Journal of Psychiatry* 153:414-416.

Glassman AH, Perel JM, Shostak M, Kantor SJ, Fleiss JL (1977). Clinical implications of imipramine plasma levels for depressive illness. *Archives of General Psychiatry* 34:197-204.

Guelfi JD, Dreyfus JF, Pichot P (1983). A double-blind controlled clinical trial comparing fluvoxamine with imipramine. *British Journal of Clinical Pharmacology* 15 (Suppl 3):411S-417S.

Guy W (1976). *Assessment manual for psychopharmacology.* Rochville: U.S. Department of Healthy Education and Welfare.

Guy W, Wilson WH, Ban TA, King DL, Manov G, Fjetland OK (1984). A double-blind clinical trial of fluvoxamine and imipramine in patients with primary depression. *Psychopharmacoly Bulletin* 20:73-78.

Hamilton M (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry* 23:56-61.

Hartter S, Wetzel H, Hammes E, Torkzadeh M, Hiemke C (1998). Nonlinear pharmacokinetics of fluvoxamine and gender differences. *Therapeutic Drug Monitoring* 20:446-449.

Hirschfeld RM (1999). Efficacy of SSRIs and newer antidepressants in severe depression: comparison with TCAs. *Journal of Clinical Psychiatry* 60:326-335.

Itil TM, Shrivastava RK, Mukherjee S, Coleman BS, Michael ST (1983). A double-blind placebo-controlled study of fluvoxamine and imipramine in out-patients with primary depression. *British Journal of Clinical Pharmacology* 15 (Suppl 3):433S-438S.

Kasper S, Moller HJ, Montgomery SA, Zondag E (1995). Antidepressant efficacy in relation to item analysis and severity of depression: a placebo-controlled trial of fluvoxamine versus imipramine. *International Clinical Psychopharmacology* 9 (Suppl 4):3-12.

Lapierre YD, Browne M, Horn E, Oyewumi LK, Sarantidis D, Roberts N, Badoe K, Tessier P (1987). Treatment of major affective disorder with fluvoxamine. *Journal of Clinical Psychiatry* 48:65-68.

Lingam R, Scott J (2002). Treatment non-adherence in affective disorders. *Acta Psychiatrica Scandinavica* 105:164-172.

Lydiard RB, Laird LK, Morton WA Jr, Steele TE, Kellner C, Laraia MT, Ballenger JC (1989). Fluvoxamine, imipramine, and placebo in the treatment of depressed outpatients: effects on depression. *Psychopharmacology Bulletin* 25:68-70.

March JS, Kobak KA, Jefferson JW, Mazza J, Greist JH (1990). A double-blind, placebo-controlled trial of fluvoxamine versus imipramine in outpatients with major depression. *Journal of Clinical Psychiatry* 51:200-202.

Nair NP, Bakish D, Saxena B, Amin M, Schwartz G, West TE (1996). Comparison of fluvoxamine, imipramine, and placebo in the treatment of outpatients with panic disorder. *Anxiety* 2:192-198.

Niklson IA, Reimitz PE, Sennef C (1997). Factors that influence the outcome of placebo-controlled antidepressant clinical trials. *Psychopharmacoly Bulletin* 33:41-51.

Norton KR, Sireling LI, Bhat AV, Rao B, Paykel ES (1984). A double-blind comparison of fluvoxamine, imipramine and placebo in depressed patients. *Journal of Affective Disorders* 7:297-308.

Spitzer R, Endicot J (1978). *Schedule for Affective Disorders and Schizofrenia (SADS)* (3rd ed). New York: Biometric Research, New York State Psychiatric Institute.

3 | A double-blind study of two-phase treatments for depressed inpatients: imipramine versus fluvoxamine, both followed by lithium addition.

In press, American Journal of Psychiatry, 2004.

Tom K. Birkenhäger
Walter W. van den Broek
Paul G.H. Mulder
Jan A. Bruijn
P. Moleman

Chapter 3.

A double-blind study of two-phase treatments for depressed inpatients: imipramine versus fluvoxamine, both followed by lithium addition.

Tom K. Birkenhäger, Walter W. van den Broek, Paul G.H. Mulder, Jan A. Bruijn, P. Moleman

Abstract

Objective:

This study was designed to compare the efficacy of 2 two-phase treatment strategies for inpatients suffering from depressive disorder according to the DSM-IV.

Method:

During phase I patients participated in a double-blind study imipramine versus fluvoxamine, with final evaluation of response 4 weeks after attaining the target plasma level. In phase II, if patients' response had been absent or partial, lithium was added to imipramine or fluvoxamine, respectively. Final evaluation of response was 3 weeks after attainment of the target lithium level (0.6-1.0 mmol/l).

Results:

Patients were enrolled in this study. At the end of phase I, remission, defined as a final HRSD score ≤ 7, was achieved by 16 of 70 (23%) of the imipramine-treated patients versus 10 of 68 (15%) of the patients on fluvoxamine. At the end of phase II, 41 of 70 (59%) of the imipramine sample versus 27 of 68 (40%) of the fluvoxamine sample qualified for remission; a significant difference in favor of the imipramine strategy. Only a small minority of both groups received concomitant medication. In both phase I and II the discontinuation rate was low (5% and 10%, respectively).

Conclusion:

In a sample of depressed inpatients imipramine with subsequent lithium addition is superior over a similar strategy with fluvoxamine. Both strategies were well tolerated.

Introduction

A substantial number of patients suffering from depressive disorder fail to respond to adequately performed treatment with antidepressants. One of the preferred treatment strategies for such refractory depression is addition of lithium to the antidepressant (Bauer and Dopfmer, 1999). The addition of lithium to an established course of an antidepressant has substantial advantages compared with strategies involving switching of antidepressants: time is saved because there is no need for tapering the previous treatment or for a wash-out period, and possible partial response to the antidepressant is preserved. Many open studies and at least 11 double-blind suggest that 50-60% of patients with refractory depression may respond to lithium-addition; two meta-analyses have confirmed the efficacy of this strategy (Austin et al., 1991; Bauer and Dopfmer, 1999; De Montigny et al., 1981; Katona et al., 1995; Stein and Bernadt, 1993). Lithium has been found to augment the therapeutic effect of several antidepressants, both tricyclic antidepressants (TCAs) (Bauer and Dopfmer, 1999) and selective serotonin reuptake inhibitors (SSRIs) (Baumann et al., 1996; Katona et al., 1995) and, possibly, venlafaxine (Hoencamp et al., 2000). There is some controversy concerning the speed of onset of the effect of lithium addition. An early open study reported a high frequency of a response within 48 hours (De Montigny et al., 1981); whereas later placebo-controlled studies have suggested that only a small minority of subjects responds within one week (Katona et al., 1995; Stein and Bernadt, 1993). A recent meta-analysis reported that maximum benefit from lithium addition is reached after 7 days (Bauer and Dopfmer, 1999).

In depressed inpatients we previously compared imipramine with mirtazepine, followed by lithium addition for nonresponders: the imipramine-lithium strategy proved to be significantly superior over mirtazepine-lithium (Bruijn et al., 1998). The present study compares imipramine with fluvoxamine, followed by lithium addition. To our knowledge no other study has compared the efficacy of lithium addition to two different antidepressants with monitoring of the response to the first phase of treatment with the antidepressants alone. This is important because the efficacy and clinical value of lithium addition can only be properly evaluated in the light of the efficacy of the first treatment step. Fluvoxamine was chosen for this study, because it has been reported to be effective in depressed inpatients (Gatti et al., 1996). The present report focuses on achieving remission during this two-phase treatment, in which phase I compares imipramine with fluvoxamine, and phase II investigates the

addition of lithium to both antidepressants for nonremitters in phase I. The results of the phase I study on imipramine versus fluvoxamine are presented elsewhere (Van den Broek et al., submitted).

Method

The study protocol was approved by the medical ethical boards of both centers and the study was performed in accordance with the ethical standards laid down in the declaration of Helsinki.

Eligible for inclusion were patients aged 18-65 years, who fulfilled DSM-IV criteria for a depressive disorder, which was diagnosed by administration of the depression part of the Schedule for Affective Disorders and Schizophrenia (SADS) (Spitzer and Endicot, 1978) and who had an HRSD score $\geq$ 17. All assessments were done by the three research psychiatrists (WWvdB, JAB, TKB). During the study, interrater sessions took place six times per year. Exclusion criteria were: schizophrenia, schizoaffective disorder, bipolar I disorder, organic brain syndrome, chronic alcohol or drug abuse, relevant somatic illness, refractoriness to previous adequate treatment with a TCA or fluvoxamine, and pregnancy or inadequate contraception for women in the fertile age group. Eligible patients had to be drug free for at least three days before baseline assessment. All patients provided written informed consent, after study procedures were fully explained.

The study was performed between April 1997 and July 2001 at the inpatient depression unit of two centers: the Department of Psychiatry, University Hospital Rotterdam (WWvdB, JAB) and Parnassia Psychomedical Center, The Hague (TKB). During the study period in the first center 201 patients met the criteria for a depressive disorder, 95 (47%) fulfilled one or more exclusion criteria and 28 (14%) patients refused participation. Thus, from the first centre 78 (39%) patients participated in the study. In the second center 145 patients met the criteria for a depressive disorder. Of these, 78 (54%) fulfilled at least one exclusion criterion and 7 (5%) patients refused participation, leaving 60 (41%) participants from the second centre. Eligible patients were then randomly allocated to double-blind treatment with either imipramine or fluvoxamine. After a 4 day single-blind placebo run-in period the 17-item HRSD was performed again. Patients still meeting inclusion criteria (HRSD reduction $\leq$ 50% and a score $\geq$ 17) started treatment with either imipramine or fluvoxamine.

Phase I: Imipramine versus fluvoxamine (5-7 weeks)

The medication comprised tablets, in two different sizes, of imipramine and fluvoxamine of identical appearance, taste and weight, containing 75 mg (the larger tablets) or 25 mg (the smaller ones) of the antidepressant.

Preparation of the study medication tablets and randomization from a random number table was done by the Department of Pharmacy of the first center. Patients received 75 mg/day of imipramine or fluvoxamine during days 1-2 and then 150 mg for days 3-8, unless any severe side effects emerged. Plasma levels of both antidepressants were monitored weekly and doses were adjusted to obtain plasma levels of 200-300 ng/ml for imipramine+ desmethylimipramine and 150-200 ng/ml for fluvoxamine. To ensure adequate blinding the Department of Pharmacy of the first center presented plasma levels as a percentage of a target plasma level. The 100% plasma level was 250 ng/ml for imipramine+desmethylimipramine and 175 ng/ml for fluvoxamine. Adequate plasma level was between 80 -120%, with the lower margin considered more important. Scoring of the 17-item HRSD and the Clinical Global Impression (CGI) of severity and response was performed weekly. Excellent interrater reliability (kappa=0.95) was achieved between the participating psychiatrists regarding the total score on the HRSD. Besides study medication, the use of concomitant psychotropic medication was strongly discouraged, although its use was not a reason for exclusion. Some patients with severe insomnia received per day 1-6 tablets containing an extract of valerian; this extract is assumed to be without antidepressant properties. A total of less than 10% of the patients received either lorazepam 1-3 mg daily for excessive anxiety, or haloperidol 1-5 mg daily for intolerable psychotic symptoms.

Phase II: Lithium addition (4-5 weeks)

Four weeks after achieving an adequate plasma level of imipramine or fluvoxamine, nonremitters had lithium added to the antidepressant. Nonremission is often defined as an HRSD score >7. For pragmatic reasons an HRSD score >13 was chosen as threshold for lithium addition: in patients with an HRSD score around 10 the adverse effects of lithium addition may well outweigh its benefits. Furthermore, in patients with entry scores below 14 the treatment effect is difficult to measure. Patients entering phase II continued their double-blind medication and had lithium added in an initial dose of 600 mg at 8 p.m. Blood lithium level was measured on day 7 and weekly thereafter, 12 hours post-dose. The dose was adjusted in order to achieve a lithium level of 0.6-1.0 mmol/l as soon as possible. Weekly assessment of the 17-item HRSD and the CGI was performed until 3 weeks after reaching the

target lithium level, at which point in time response was evaluated. Weekly measurement of antidepressant plasma level continued throughout phase II. Similar to phase I, the use of concomitant psychotropic medication, although permitted, was strongly discouraged.

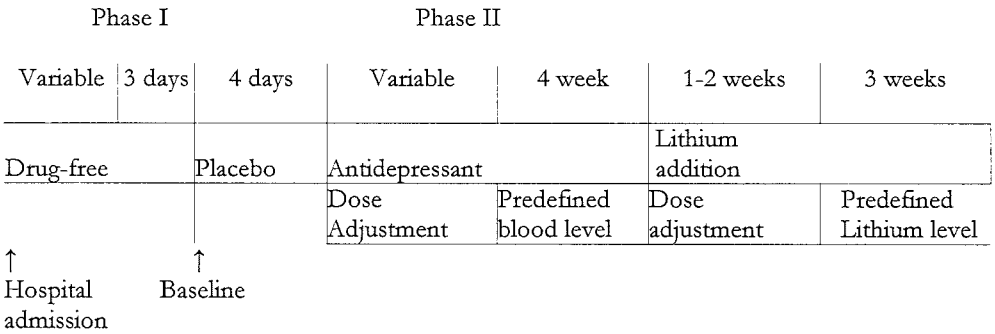


Figure 1. General outline of the study design

Statistical analysis

The efficacy of both treatment strategies was compared with survival analysis using the Cox Proportional Hazards Model. The duration of treatment until the response criterion was met is the survival time variable. Two outcome criteria were used: response and remission. Response was defined as a reduction in the HRSD score of at least 50% compared to baseline. Remission required a post treatment HRSD score ≤ 7.

During phase I the HRSD was assessed weekly, until 4 weeks after achieving the target antidepressant plasma level, and during phase II until 3 weeks after attainment of an adequate blood lithium level. The first time a patient met the response criterion is scored as a terminal event. Drop-outs were censored at the time of drop-out. Nonresponders were censored at the end of phase II. The following prespecified covariables were included with the treatment strategy: center, the duration of the index episode, adequate previous treatment during the index episode, and the presence of psychotic features. Adequate previous treatment during the index episode is defined as a score ≥ 3 on the Antidepressant Treatment History Form (Prudic et al., 1996; Sackeim et al., 1990). A p-value < 0.05 (two-sided) is considered statistically significant.

Results

Study sample

A total of 138 depressed inpatients were randomly assigned to either imipramine (N=70) or fluvoxamine (N=68), of whom 131 were completers. The mean±SD daily doses after achieving the target plasma level were 253±77 (range: 75-450) mg for impramine and 287±265 (range: 150-1800) mg for fluvoxamine. 36 of 70 (51%) patients on imipramine and 23 of 68 (34%) patients on fluvoxamine were responders. Remission was achieved by 20/70 (28.6%) patients on imipramine versus 12/68 (17.6%) patients on fluvoxamine. Of the 131 Phase I completers, 78 (59%) met the inclusion criteria for phase II and 71 of them received lithium addition. Although meeting the entry criteria for phase II, 7 patients did not participate: 3 received electroconvulsive therapy because of a deteriorating condition, 2 discharged themselves without our consent, and 2 patients refused lithium addition. Table 1 gives the demographic and clinical characteristics of the138 study participants. The two treatment groups were balanced for age, sex, entry HRSD score and the proportion of patients with psychotic features. During phase II 4 patients on imipramine-lithium dropped out: 1 due to adverse effects, another because of hypomania, and 2 others refused further cooperation. Three patients on fluvoxamine-lithium dropped out: 1 due to a deteriorating condition, one discharged without our consent and 1 patient had an emerging somatic illness. The total drop-out rate for phase II was 7/71 (10%) (Table 2). Finally, 64 patients completed phase II, 31 patients on imipramine and 33 on fluvoxamine.

Table 1. Demographic and clinical characteristics of the study population

Variable	Imipramine	Fluvoxamine
Number of patients (N)	70	68
Age (years), range	19-65	27-65
Age (years), mean±SD	49.8±13.5	52.6±9.9
Sex, M/F	27/43	18/50
Duration index episode >1 year N (%)	24 (34%)	32 (47%)
Adequate pretreatment with Antidepressants, N (%)	31 (44%)	29 (42%)
Psychotic features, N (%)	25 (36%)	23 (33%)
Baseline HRSD score, mean±SD	25.7±4.8	25.5±5.0
Antidepressant dose, mean±SD (mg/day)	221±85	214±151
Antidepressant plasma level (ng/ml)	263±92	193±72

Table 2. Discontinuation during antidepressant monotherapy (phase I) and lithium addition (phaseII)

Antidepressant	Reason for drop-out	N
Imipramine		
Phase I	Adverse effects	3
	Worsening	2
Phase II	Hypomania	1
	Non-compliance	2
	Adverse effects	1
Fluvoxamine		
Phase I	Adverse effects	1
	Discharge without our consent	1
Phase II	Emerging illness	1
	Discharge without our consent	1
	Worsening	1

Plasma antidepressant and lithium levels

Antidepressant plasma levels are available for all 138 patients who took study medication. The mean plasma level after achieving the target level was 262.7±93 ng/ml for imipramine (n=70) and 193.2±71.8 ng/ml for fluvoxamine (n=68). The mean±SD time to achieve the target plasma level was 13.3±4.4 days for imipramine and 12.6±6.2 days for fluvoxamine.

Plasma lithium levels are available for 68 out of the 71 (96%) patients starting on lithium, because three patients dropped out before the first plasma level determination. Mean lithium level after achieving the target level was 0.81± 0.13 mmol/l for the imipramine group and 0.78±0.14 mmol/l for the fluvoxamine group. Six patients, 2 on imipramine and 4 on fluvoxamine, completing phase II had a lithium level < 0.6 mmol/l on at least one occasion, while only one patient on fluvoxamine had a final lithium level < 0.6 mmol/l (0.53 mmol/l). The mean ± SD time to attain target lithium level was 15.5±6.3 days.

Concurrent medication

During phase I, 12 of 138 patients (9%) received concurrent medication. Lorazepam was prescribed to 4 patients on imipramine and 5 on fluvoxamine. Three of the 48 patients suffering from psychotic depression were treated with 2.5-10

mg/day haloperidol; 1 patient on imipramine and 2 on fluvoxamine, all three were nonresponders at the end of phase I. During phase II, 7 of 71 patients (10%) were treated with concurrent medication. Two patients in each sample received lorazepam. Three patients on fluvoxamine-lithium received haloperidol, neither of them responded at the end of phase II.

Efficacy

Response (50% decrease in HRSD score) occurred in 50 of 70 (71%) of patients on imipramine and lithium versus 44 of 68 (64%) patients on fluvoxamine and lithium. Remission was achieved in 41 of 70 (59%) patients in the imipramine sample versus 27 of 68 (40%) patients in the fluvoxamine sample. The mean±SD reduction in HRSD score during phase I and II together was 13.8 ±9.3 for imipramine and 11.9 ± 9.2 for fluvoxamine, which is a nonsignificant difference. The Cox regression analysis of response in the total sample (N=138) for phase I and II together, with the type of treatment as independent variable and adjusted for the prespecified covariables shows no significant difference (p= 0.22; 95% CI: 0.51-1.17). The Cox regression analysis of remission of the total population revealed a significant difference between the two treatment samples in favor of the imipramine strategy (p=0.049; 95% CI: 0.37-0.99). The probability of nonresponse of the two treatment groups over time is shown by two curves of the Cox regression analyses in Figures 2 and 3. None of the prespecified covariables (center, presence of psychotic features, duration of the index episode over one year and adequate pre-treatment of the index episode) shows a significant effect on the difference found between imipramine and fluvoxamine.

Considering phase II separately, the efficacy of lithium addition is high in both treatment groups. The remission rate in imipramine non-remitters is 25/35 (71%) and in fluvoxamine non-remitters 17/36 (47%).

A considerable proportion of patients met the criteria for response after only 1 week of lithium addition. Ten of 31 (33%) patients in the imipramine sample and 7 of 33 (26%) fluvoxamine treated patients responded after 1 week of lithium addition. No significant difference in response at this point in time was found between the two treatment groups. Another 30 patients responded during the remaining weeks of lithium addition, compared to 17 patients in the first week. Thus, the early responders constitute about one third of the overall number of Phase II responders.

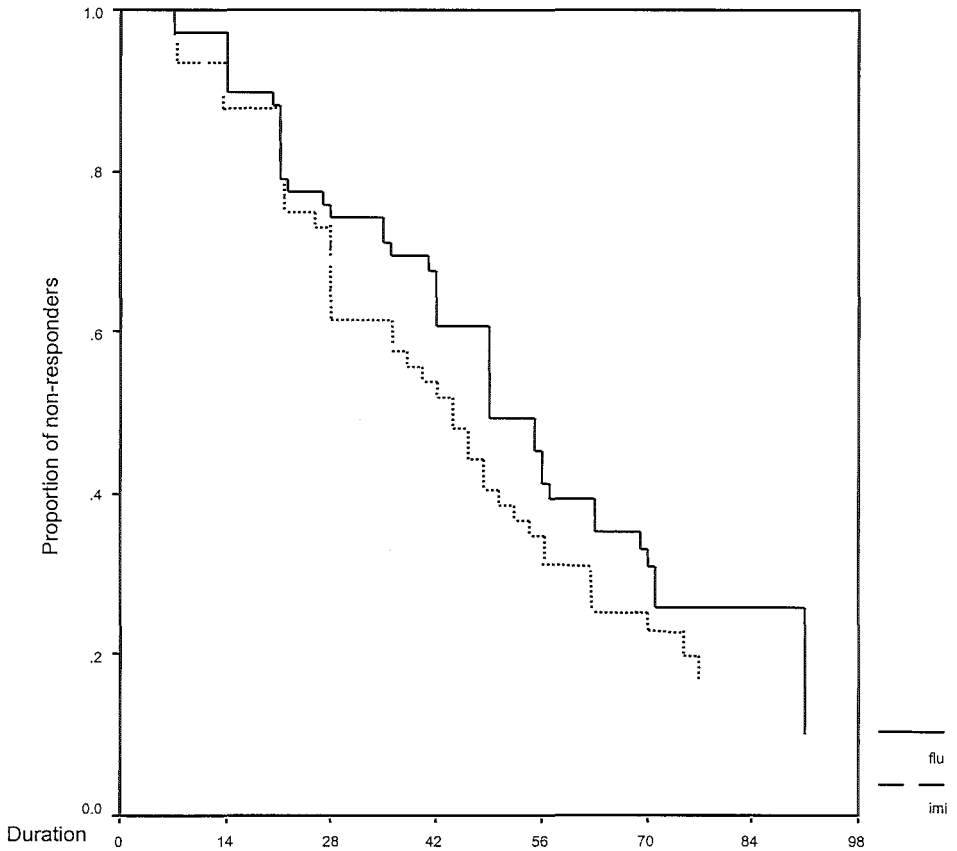


Figure 2. Survival analysis for time to response (HRSD↓ ≥ 50%)

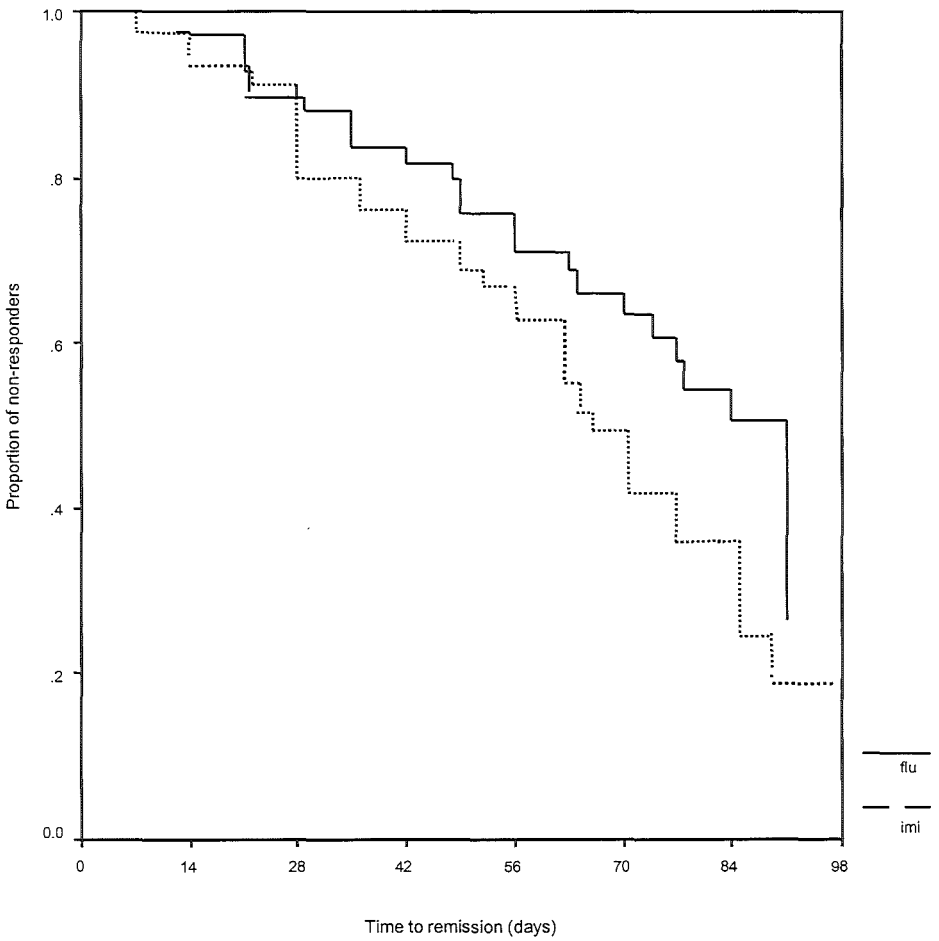


Figure 3. Probability of not achieving remission (HRSD ≤ 7) for the two treatment groups over time (p=0.049)

Table 3. Intent-to-Treat response at the end of phase II

Response at the end of Phase I and Phase II according to the ≥ 50% reduction in HRSD score		
Response	Imipramine	Fluvoxamine
Phase I N	28/70 (40%)	19/68 (28%)
Phase II N	50/70 (71%)	44/68 (64%)
Person-weeks	395	457
Remission at the end of phase I and phase II according to final HRSD score ≤ 7		
Phase I N	16/70 (23%)	10/68 (15%)
Phase II N	41/70 (59%)	27/68 (40%)
Person-weeks	494	539

Table 4. Influence of treatment and covariables on remission

Variable	Hazard ratio	p-value	95% Confidence Interval
Type of treatment (fluvoxamine)	0.60	0.049	0.37 to 0.99
Psychotic features (yes)	0.95	0.84	0.57 to 1.57
Duration index episode (>1y)	0.45	0.008	0.25 to 0.81
Adequate pretreatment (yes)	0.70	0.70	0.41 to 1.19

Discussion

Lithium addition is recommended as a first choice for depressed patients who do not respond to therapy with conventional antidepressants (Bauer and Dopfmer, 1999), which is in line with the Practice Guidelines of the American Psychiatric Association ("Practice guideline for the treatment of patients with major depressive disorder (revision). American Psychiatric Association," 2000). The present study is the first to provide meaningful quantification to the effect of lithium addition, because prior treatment with both antidepressants was controlled for in the first phase of the study. In addition, the present study provides a comparison between imipramine and fluvoxamine, followed by lithium addition in patients not achieving remission with either agent. Efficacy of lithium addition can be evaluated properly only if treatment with the antidepressant in the first phase is optimal, including dosing. This was achieved in the first phase of this study (Sackeim et al., 1990; Van

den Broek et. al., submitted). The remission rate of lithium addition was 71% in the imipramine sample (25 of 35 non-remitters in phase I) and 47% in the fluvoxamine sample (17 0f 36 non-remitters in phase I). Our figures are even more favorable than the 50% usually cited for the efficacy of lithium addition ("Practice guideline for the treatment of patients with major depressive disorder (revision). American Psychiatric Association," 2000), as far as imipramine is concerned. In clinical practice lithium will most often be added to the antidepressant that did not provide sufficient response. Therefore, it is important that the two-step treatment with imipramine and lithium is more effective than with fluvoxamine and lithium, remission rates being 59% (41 of 70 patients included in phase I) and 40% (27 of 68 patients included in phase I). In the present study, the difference is not as large as it is between the two-step treatment with imipramine and lithium compared with mirtazapine and lithium (Bruijn et al., 1998); both these studies concerned severely depressed inpatients, of whom 35% and 32%, respectively, had psychotic features. In the present study, about one in three patients responded to lithium addition during the first week, which is in accordance with a recent meta-analysis (Bauer and Dopfmer, 1999). Lithium addition should, therefore, be considered as the preferred second-treatment step in severely depressed (in)patients, because it may even induce a faster response than electroconvulsive therapy (Dinan and Barry, 1989). Almost 60% of our patients were in remission after the 9-12 weeks of this two-step treatment with imipramine and lithium, and more than 70% responded. This high percentage of patients in remission is important in view of the vulnerability of patients with residual symptoms for relapse (Paykel, 1998). As also reported by others, our patients with a longer duration of the present episode showed significantly less response and remission, not only after treatment with the antidepressant, but also after addition of lithium. However, neither this covariable, nor "adequate pretreatment", nor "psychotic features" contributed significantly to the difference between the two-step treatments with imipramine or fluvoxamine. The two-step treatment with imipramine resulted in a slightly higher discontinuation rate, (13%) compared to fluvoxamine (7%), although in absolute numbers the difference is small. The SSRI-lithium combination was tolerated well (Baumann et al., 1996; Katona et al., 1995), with no indications for a substantial risk of a serotonin syndrome described previously during fluvoxamine-lithium treatment (Ohman and Spigset, 1993).

The overall response rate and remission rate during phase I were relatively low, 34% and 19%, respectively. This may be due to the inclusion of many patients that had been pretreated with antidepressants and/or were referred to inpatient units specialized in the treatment of severe and often resistant depression. This makes the

remission rate of 50% on lithium addition the more remarkable and clinically relevant. The dose of both antidepressants was adjusted in order to attain a target plasma level. This could be considered a disadvantage for the fluvoxamine-treated sample, because no plasma level-response relationship has been proven in contrast with imipramine (Perry et al., 1987). This does not seem likely, however, since the mean daily dose for fluvoxamine was relatively high (287 mg) and the target plasma level technique itself results in excluding low and possibly subtherapeutic plasma levels in fast metabolizers of fluvoxamine (Bauer et al., 2002).

In conclusion, treatment with imipramine with plasma level targeted dosing and addition of lithium for nonremitters proved to be a highly effective treatment for our severely depressed inpatients, including those with psychotic features. It is slightly, but significantly, more effective than the same two-step treatment with the SSRI fluvoxamine; the difference compared with the two-step treatment with mirtazapine is more pronounced (Bruijn et al., 1998). This is at the expense of a higher discontinuation rate with imipramine, but this rate is only about 10%. We, therefore, consider imipramine with plasma level targeted dosing and lithium addition for nonremitters to be first choice in the treatment of these patients. Since a similar two-step treatment with fluvoxamine is not very much less effective and leads to less discontinuation, fluvoxamine as a first choice is justifiable, especially in less severely depressed patients.

References

Austin MP, Souza FG, Goodwin GM (1991). Lithium augmentation in antidepressant-resistant patients. A quantitative analysis. *British Journal of Psychiatry* 159:510-514.

Bauer M, Dopfmer S (1999). Lithium augmentation in treatment-resistant depression: meta-analysis of placebo-controlled studies. *Journal of Clinical Psychopharmacology* 19:427-434.

Bauer M, Whybrow PC, Angst J, Versiani M, Moller HJ (2002). World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 1: Acute and continuation treatment of major depressive disorder. *World Journal of Biological Psychiatry* 3:5-43.

Baumann P, Nil R, Souche A, Montaldi S, Baettig D, Lambert S, Uehlinger C, Kasas A, Amey M, Jonzier-Perey M (1996). A double-blind, placebo-controlled study of citalopram with and without lithium in the treatment of therapy-resistant depressive patients: a clinical, pharmacokinetic, and pharmacogenetic investigation. *Journal of Clinical Psychopharmacology* 16:307-314.

Bruijn JA, Moleman P, Mulder PG, Van den Broek WW (1998). Comparison of 2 treatment strategies for depressed inpatients: imipramine and lithium addition or mirtazapine and lithium addition. *Journal of Clinical Psychiatry* 59:657-663.

De Montigny C, Grunberg F, Mayer A, Deschenes JP. (1981). Lithium induces rapid relief of depression in tricyclic antidepressant drug non-responders. *British Journal of Psychiatry* 138:252-256.

Dinan TG, Barry S (1989). A comparison of electroconvulsive therapy with a combined lithium and tricyclic combination among depressed tricyclic nonresponders. *Acta Psychiatrica Scandinavica* 80:97-100.

Gatti F, Bellini L, Gasperini M, Perez J, Zanardi R, Smeraldi E (1996). Fluvoxamine alone in the treatment of delusional depression. *American Journal of Psychiatry,* 153:414-416.

Hoencamp E, Haffmans J, Dijken WA, Huijbrechts IP (2000). Lithium augmentation of venlafaxine: an open-label trial. *Journal of Clinical Psychopharmacology* 20:538-543.

Katona CL, Abou-Saleh MT, Harrison DA, Nairac BA, Edwards DR., Lock T, Burns RA, Robertson MM (1995). Placebo-controlled trial of lithium augmentation of fluoxetine and lofepramine. *British Journal of Psychiatry* 166:80-86.

Ohman R, Spigset O (1993). Serotonin syndrome induced by fluvoxamine-lithium interaction. *Pharmacopsychiatry* 26:263-264.

Paykel ES (1998). Remission and residual symptomatology in major depression. *Psychopathology* 31:5-14.

Perry PJ, Pfohl BM, Holstad SG (1987). The relationship between antidepressant response and tricyclic antidepressant plasma concentrations. A retrospective analysis of the literature using logistic regression analysis. *Clinical Pharmacokinetics* 13:381-392.

Practice guideline for the treatment of patients with major depressive disorder (revision). American Psychiatric Association. (2000). *American Journal of Psychiatry* 157 (Suppl):1-45.

Prudic J, Haskett RF, Mulsant B, Malone KM, Pettinati HM, Stephens S, Greenberg R, Rifas SL, Sackeim HA (1996). Resistance to antidepressant medications and short-term clinical response to ECT. *American Journal of Psychiatry* 153:985-992.

Sackeim HA, Prudic J, Devanand DP, Decina P, Kerr B, Malitz S (1990). The impact of medication resistance and continuation pharmacotherapy on relapse following response to electroconvulsive therapy in major depression. *Journal of Clinical Psychopharmacology* 10:96-104.

Spitzer R, Endicot J (1978). *Schedule for Affective Disorders and Schizofrenia (SADS)* (3rd ed). New York: Biometric Research, New York State Psychiatric Institute.

Stein G, Bernadt M (1993). Lithium augmentation therapy in tricyclic-resistant depression. A controlled trial using lithium in low and normal doses. *British Journal of Psychiatry* 162:634-640.

4 | Efficacy and tolerability of tranylcypromine versus phenelzine: a double-blind study in antidepressant-refractory depressed in-patients

In press, Journal of Clinical Psychiatry, 2004

Tom K. Birkenhäger
Walter W. van den Broek
Paul G.H. Mulder
Jan A. Bruijn
Peter Moleman

Chapter 4.

Efficacy and tolerability of tranylcypromine versus phenelzine: a double-blind study in antidepressant-refractory depressed inpatients

Tom K. Birkenhäger, Walter W. van den Broek, Paul G.H. Mulder, Jan A. Bruijn, Peter Moleman

Abstract

Background:

The aim of this study was to examine whether phenelzine is a suitable alternative to tranylcypromine in antidepressant-resistant depression.

Method:

A total of 77 severely depressed inpatients who failed to respond to fixed plasma level treatment with either tricyclic antidepressants or fluvoxamine were withdrawn from psychotropic medication and included in a double-blind flexible-dose 5-week comparison of tranylcypromine and phenelzine.

Results:

Of the 77 patients, 67 (87%) completed the trial, of whom 34 (51%) responded.

No significant differences in response between both drugs were observed. Seventeen of 39 (44%) patients responded to tranylcypromine and 18/38 (47%) to phenelzine (≥50% reduction in Hamilton Rating Scale for Depression score).

The mean reduction in HRSD score was 10.4±8.3 for the tranylcypromine sample versus 8.3±8.4 for the phenelzine-treated patients. Only a few patients (10%) used concomitant psychotropic medication. A substantial number of patients experienced severe side-effects, mainly dizziness, agitation and insomnia; the incidence was the same in both samples (21%).

Conclusion:

No difference in efficacy was observed between both monoamine oxidase inhibitors in a sample of patients with severe antidepressant-refractory depression. Phenelzine appears to be a suitable alternative to tranylcypromine.

Keywords:

Tranylcypromine; phenelzine; refractory depression; treatment-resistant depression; monoamine oxidase inhibitor.

Introduction

The use of non-selective monoamine oxidase inhibitors (MAOIs) is limited by several factors, particularly dietary restrictions, reports of toxic interactions, and their supposed inferior efficacy in patients with melancholic depression in comparison with tricyclic antidepressants (TCAs) (Nolen, 1997).

MAOIs are used frequently in the treatment of depressed patients that have not responded to TCAs. Several uncontrolled open studies (Amsterdam and Berwish, 1989; Roose et al., 1986; Thase et al., 1992) have supported the efficacy of tranylcypromine in tricyclic antidepressant (TCA)-refractory depression.

Nolen et al. found tranylcypromine to be superior over both L-5HTP in an open randomised study (Nolen et al., 1985) and nomifensine in a double-blind study (Nolen et al., 1988). In both those studies, 50 percent of the highly refractory patients responded to tranylcypromine. A similar efficacy was reported after a double-blind comparative study with the reversible inhibitor of MAO-A (RIMA) brofaromine (Nolen et al., 1993) . Two other double-blind studies found an even higher efficacy (about 75%) for tranylcypromine in refractory depression (Thase et al., 1992; Volz et al., 1994). However, a considerable proportion of patients on tranylcypromine experiences serious adverse effects, such as orthostatic hypotension, agitation and insomnia. There clearly is a need for an effective MAOI which is better tolerated than tranylcypromine. The RIMA brofaromine may have been a promising alternative to tranylcypromine (Nolen et al., 1993; Volz et al., 1994), but has been withdrawn from further development. Another RIMA, moclobemide, has not been well studied in refractory depression; according to the clinical impression of some investigators (Fahy, 1993; Vink et al., 1994) it probably is not an effective alternative to tranylcypromine.

Both tranylcypromine and phenelzine are irreversible inhibitors of both the A and B form of the MAO enzyme. Phenelzine has been studied most extensively in so-called atypical depression. This type of depression requires preserved reactivity of mood and at least two additional atypical symptoms. A series of studies carried out by the Columbia University in New York (for review, see (Quitkin et al., 1993)) showed phenelzine to be superior over both placebo and imipramine in outpatients with atypical depression. Phenelzine has been studied in outpatients with atypical

depression that had not responded to a TCA (McGrath et al., 1987) but studies in TCA-refractory inpatients with melancholic depression are lacking.

Phenelzine and tranylcypromine show differences in both chemical structure and pharmacological characteristics. In contrast with phenelzine, tranylcypromine is not a hydrazine derivative and is structurally related to amphetamine. Tranylcypromine is more likely to provoke a hypertensive reaction (Blackwell, 1991).

Aim of the study

The present study consists of a double-blind comparison of tranylcypromine versus phenelzine in antidepressant-refractory severely depressed inpatients. This study is the first to compare the efficacy of these two MAOIs. It was designed to assess, whether phenelzine might be a suitable alternative to tranylcypromine in patients with severe antidepressant-refractory depression.

Method

The study was performed between November 1996 and July 2001 at the inpatient depression unit of two centres: Parnassia Psychomedical Centre, The Hague (TKB) and the Department of Psychiatry, Erasmus University Hospital Rotterdam, (WWvdB, JAB). Both units have a supraregional function for the treatment of treatment-resistant depressed patients. It is routine practice to discontinue psychotropic drugs after admission. Depressed patients were screened for in- and exclusion criteria. The study protocol was approved by the medical ethical boards of both centres and the study was conducted in accordance with the Declaration of Helsinki. Eligible patients provided written informed consent after study procedures were fully explained.

Patient selection

The study was a 5-week randomized double-blind comparison of tranylcypromine and phenelzine, preceded by a wash-out of 1 week. Included were inpatients aged 18-65 years with a depressive disorder according to the DSM-IV criteria and a score $\geq$ 14 on the 17-item Hamilton Rating Scale for Depression (HRSD) (Bech et al., 1986). Furthermore they were nonresponders to either a double-blind fixed plasma level study with imipramine versus fluvoxamine, or open treatment with a TCA with adequate plasma levels. All patients had achieved stable plasma levels of $\geq$ 200 ng/ml for imipramine+desmethylimipramine, $\geq$ 150 ng/ml

for fluvoxamine, ≥ 100 ng/ml for amitriptyline+nortriptyline, ≥ 150 ng/ml for clomipramine+desmethylclomipramine, or 50-150 ng/ml for nortriptyline during 4 weeks. Excluded were patients with schizophrenia, bipolar or schizo-affective disorder, organic brain syndrome, chronic alcohol or drug use, relevant somatic illness, pregnancy or inadequate contraception for women in the fertile age, refractoriness to previous adequate treatment with an MAOI, or an immediate indication for electroconvulsive therapy. None of the patients had been using fluoxetine in the five weeks before study entry. Preparation of the study medication capsules and randomization from a random number table was done by the Department of Pharmacy of the second centre.

Treatments

Antidepressants were withdrawn at least one week before the start of the MAOI .

The study medication comprised capsules of tranylcypromine and phenelzine of identical appearance, taste and weight, containing 10 mg of the MAOI.

Treatment was started at a daily dose of 20 mg, divided in two equal dosages given at 8.00 a.m. and 8.00 p.m. After 3, 7, 10 and 14 days, the daily doses could be increased to 40, 60, 80 and 100 mg, respectively, in case of insufficient response (i.e. HRSD reduction by less than 50%). When side-effects were severe, doses were not increased or decreased. Moreover, dihydroergotamine could be given in case of orthostatic hypotension. The use of concurrent psychotropic medication was prohibited, with the exception of lorazepam (maximum dose 3 mg daily). All patients were kept on a tyramine-restricted diet.

Study assessments

The diagnosis was assessed by performing the depression part of the Schedule for Affective Disorders and Schizophrenia (SADS) (Spitzer and Endicot, 1978). The severity of depression was scored weekly on both the HRSD and the Clinical Global Impression (CGI) of severity and response.

All assessments were done by the three research psychiatrists (WWvdB, JAB, TKB). To ensure comparable ratings, interrater reliability sessions took place six times per year during the study.

Excellent interrater reliability (kappa=0.95) was achieved between the participating psychiatrists regarding the total score on the HRSD.

In all patients, blood pressure and pulse rate were measured twice daily both in lying and standing position at 7.00 a.m. and 9.00 p.m. The well-known side-effects of both MAOIs were evaluated weekly, i.e. dizziness, headache, agitation, drowsiness

and insomnia. In addition, other spontaneously reported side-effects were also recorded. When side-effects either prevented dose increment or led to the prescription of concurrent medication they were rated "severe". Side-effects were considered present when they appeared or worsened after baseline.

Statistical analysis

The primary response criteria were defined a priori as a reduction of at least 50% of the HRSD score compared to baseline, an HRSD final score ≤ 7, and "much improved" or "very much improved" on the CGI, respectively. All statistical analyses are intent-to-treat analyses, for patients who dropped-out the score of the last week with treatment is carried forward to week 5. Dichotomous variables are analyzed with Fisher's exact test; the t-test is used for comparing continuous variables with a Gaussian-shaped distribution. For the response definition 50% reduction in the HRSD score we analyzed the difference in time to response between the two treatment groups, using a Cox proportional hazards model. The duration of treatment until the response criterion was met is the survival time variable. Dropouts were censored at the time of dropout. Analysis for testing difference in response between the two treatments was adjusted for three prespecified co-variables (duration of the index episode, psychotic features, and previous treatment during index episode) and stratified for centre.

Mean reduction in the HRSD score week 5 compared to baseline was compared between the two treatment samples using analysis of covariance (ANCOVA) with the baseline HRSD score as covariate. CGI improvement scores between the two samples were compared using logistic regression including the prespecified covariables mentioned above. With regard to tolerability, we assumed that if one of the MAOIs would cause more serious adverse effects this could lead to a higher discontinuation rate or to suboptimal dosing in nonresponders. Therefore we analyzed both dropout rate and final MAOI dose in nonresponders. Statistical significance was defined as $p<0.05$. Statistical analyses were performed using SPSS for Windows, version 10 (SPSS Inc., Chicago, Ill.)

Results

Of the 59 eligible patients with an antidepressant-refractory depressive disorder at the first center (Parnassia), 8 (14%) patients fulfilled one ore more exclusion criteria, 6 (10%) patients refused participation and 45 (76%) patients participated. In the second center (Erasmus MC) 50 patients were diagnosed with an antidepressant-

refractory depressive disorder, of which 15 (30%) fulfilled at least one exclusion criterion, 3 (6%) refused participation and 32 (64%) patients participated (Figure 1).

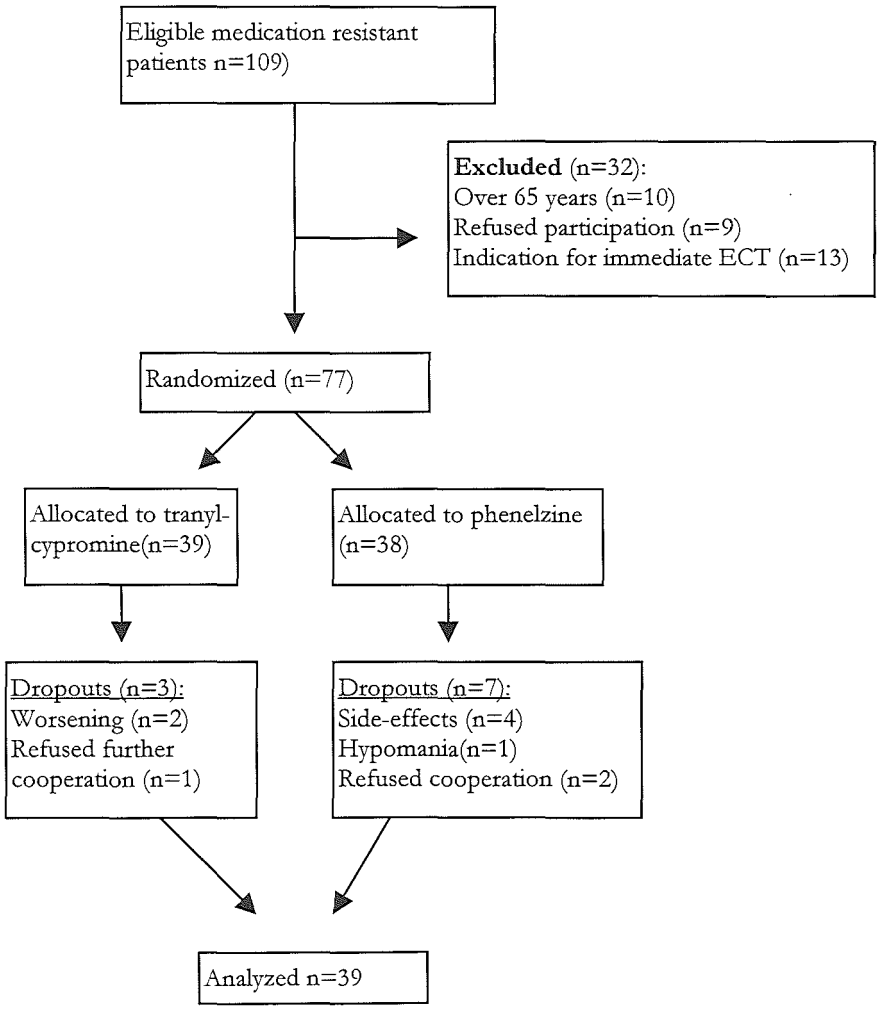


Figure 1. Participant flow.

A total of 77 depressed inpatients were randomly assigned to either tranylcypromine (N=39) or phenelzine (N=38). Twenty-three patients (30%) had been nonresponders to fixed plasma level treatment with imipramine or fluvoxamine (van den Broek, Birkenhager, Mulder, Bruijn, & Moleman, 2004), followed by lithium addition. The remaining 54 patients (69%) had not responded to open treatment with a TCA with therapeutic plasma levels. Subclassification according to the DSM-IV reveals that 23 patients (30%) were suffering from depression with mood congruent psychotic features. Table 1 gives the demographic and clinical characteristics of the total sample. The two treatment groups were balanced for age, previous treatment and entry HRSD score. There was a nonsignificant greater number of males in the tranylcypromine-treated sample (13 and 8, respectively). Moreover, there was a trend towards patients with psychotic features being overrepresented in the tranylcypromine-treated sample (16 versus 7; p=0.06).

Table 1. Demographic and clinical characteristics of the study sample

Variable	Tranylcypromine	Phenelzine	Total
No. of patients	39	38	77
Age (years), range	31-65	32-64	31-65
Age (years), mean±SD	54.1±8.7	53.1±9.5	53.6±9.0
Sex, M/F	13/26	8/30	21/56
Prior nonresponse to lithium addition, N (%)	12 (31%)	11 (29%)	23 (30%)
Duration index episode> 1 year, N (%)	21 (54%)	26 (68%)	47 (61%)
Psychotic features, N (%)	16 (41%)	7 (18%)	23 (30%)
Baseline HRSD score, mean±SD	27.2±4.9	25.7±4.2	26.5±4.6
Dose of nonresponders, mean±SD (mg/day)	50.5±3.2	77.4±2.8	-

Response to treatment

With response defined as a 50% reduction in the HRSD score, 17 of 39 (44%) patients on tranylcypromine and 18 of 38 (47%) patients on phenelzine were responders (Fisher's exact test: p=0.82).

Only 7 of 39 patients (18%) on tranylcypromine and 4 of 38 patients (11%) on phenelzine met the criterion for remission, defined as a final HRSD score ≤7 (Fisher's exact test: p=0.52). The mean reduction in HRSD score ± SD was 10.4 ±

8.3 for the tranylcypromine sample versus 8.3 ± 8.4 for the phenelzine-treated patients (ANCOVA phenelzine-tranylcypromine = -2.34, Standard Error (SE) =1.94, df =76, p=0.23).

With response defined as a ≥ 50% reduction of in the HRSD score, the Cox proportional hazards model, stratified for centre with adjustment for three prespecified covariables (previous antidepressant treatment, psychotic features, and duration of the index episode) showed no significant difference in time to response (hazard ratio=1.01, 95% CI: 0.54-1.99, p=0.97).

Sixteen of 39 (41%) patients on tranylcypromine and 15 of 38 (39%) patients on phenelzine met the response criterion "much improved" or "very much improved" on the CGI (likelihood ratio test; p=0.94).

Thus, no differences in efficacy between the two drugs were detected.

Table 2. Discontinuation during MAOI treatment

MAOI	Reason for dropout	N
Tranylcypromine	Worsening	2
	Non-compliance	1
Phenelzine	Worsening	4
	Non-compliance	1
	Hypomania	1
	Adverse effects	1

Table 3. Influence of treatment and covariables on response

	Hazard ratio	p-value	95% Confidence interval
Type of treatment (tranylcypromine)	1.01	0.97	0.52 to 1.98
Psychotic features (yes)	0.73	0.42	0.34 to 1.56
Duration of index episode (>1year)	0.89	0.76	0.43 to 1.83
Pretreatment with lihium addition (yes)	0.79	0.53	0.37 to 1.66

Atypical features

Six patients (8%) showed a preserved reactivity of mood, which is the core symptom of atypical depression. One of them met the criteria for definite atypical depression, which requires two additional criteria. Another suffered from probable

atypical depression, which requires one additional criterion. The overall MAOI response of these mood-reactive patients was 5/6 (83%).

Concomitant medication

Four patients on tranylcypromine (4/39) and three patients on phenelzine (3/38) were prescribed lorazepam 1-2 mg daily for intolerable anxiety. One of seven psychotic patients on phenelzine was treated with 3 mg haloperidol. The total number of patients using concurrent psychotropic medication was 8/77 (10.3%), which has been ignored in the analyses because of the small number of patients.

Dropouts

Ten patients did not complete the study, 3 patients on tranylcypromine (3/39=8%) and 7 on phenelzine (7/38=18%). Thus, the overall discontinuation amounts to 10 of 77 (13%). Six patients (2 on tranylcypromine and 4 on phenelzine) dropped out due to a deteriorating condition. One patient on phenelzine dropped-out because of hypomania, and three patients (2 on phenelzine) refused further cooperation.

Adverse effects

Only one patient on phenelzine dropped out due to adverse effects. Nevertheless, side-effects were a major cause for concern, since severe forms of dizziness, agitation and insomnia were reported by 21% of the patients. The frequency of these adverse effects was virtually the same in both samples. Severe drowsiness occurred more frequently with phenelzine than with tranylcypromine; however, not at a significant level.

Table 4. Serious adverse effects

	Tranylcypromine (n=39)	Phenelzine (n=38)
Severe dizziness	7 (18%)	7 (18%)
Severe agitation	8 (21%)	7 (18%)
Severe headache	4 (10%)	3 (8%)
Severe drowsiness	0 (0%)	3 (8%)
Severe insomnia	8 (21%)	6 (16%)

Doses

The mean daily dose in the total sample was 60.5±2.9 mg for tranylcypromine and 79±2.7 mg for phenelzine (2-tailed Mann-Whitney test; p=0.004).

The mean daily dose in nonresponders was 50.5±3.2 mg for tranylcypromine and 77.4±2.8 mg for phenelzine (2-tailed Mann-Whitney Test; p=0.012). Side-effects prevented dose increment in 8 patients on tranylcypromine and 5 on phenelzine.

Discussion

In this report we describe the first randomized study to compare the efficacy and tolerability of phenelzine with that of tranylcypromine in severe antidepressant-refractory depression. No indication of differences in efficacy between both MAOIs was found. The present study has limited power to detect such differences and definite conclusions should await the results of larger studies. The strict criteria required for treatment resistance restrict the number of patients available for such studies; therefore it is questionable whether a larger study than the present one will ever be performed. The overall intent-to-treat MAOI response (45%) in our study can be considered a satisfactory result in patients with severe treatment-resistant depression and is comparable with the results of previous studies (Thase and Rush, 1995). In such treatment-resistant patient samples a placebo response is assumed to be 10% by some investigators (Thase et al., 1994). If we would agree with this assumption, the efficacy of both MAOIs in the present study is beyond doubt. The response rate amounts to 40-50% for both MAOIs (HRSD: 45.5%; CGI: 40.3%). The mean reduction in HRSD score was larger in the tranylcypromine sample (10.4 versus 8.3), but not at a significant level. Since the present study has a flexible-dose design, nonresponders could be expected to receive high doses (90-100 mg of either compound), unless side-effects would have prevented increasing the dose. Apparently, the mean dose in nonresponders to tranylcypromine was significantly lower compared with phenelzine nonresponders. This probably reflects a better tolerability of phenelzine, even though the number of patients suffering from severe adverse effects did not differ between both samples.

Furthermore, the relatively low dose in nonresponders to tranylcypromine may have prevented the exertion of its full therapeutic potential in some patients. The optimal dosages for MAOI treatment are not exactly known. According to an extensive meta-analysis (Thase et al., 1995) there is no evidence to support the efficacy of MAOIs at daily doses lower than 30 mg for tranylcypromine and 45 mg for phenelzine. Since further information is lacking it is impossible to examine

whether the dosages used in the present study were optimal.

Thus, our results may hint at a slightly better efficacy and a slightly worse tolerability of tranylcypromine. Concerning various illness characteristics, patients with a longer duration of the index episode and/or psychotic features showed reduced response, but not at a significant level. A remarkably high MAOI response rate (5/6= 83%) was found in patients with preserved reactivity of mood, which is known to be the core symptom of atypical depression; this is in accordance with previous studies (Quitkin et al., 1993). However, the number of patients manifesting these features was small, which is not surprising in an inpatient setting (Nolen et al., 1988).

In conclusion, treatment with both MAOIs proved to be effective in our sample of severely depressed inpatients that had been refractory to previous treatment with antidepressants, including those patients with psychotic features. Our results provide further support for treatment with non-selective MAOIs if the depression did not respond to TCAs and other antidepressants. Because tranylcypromine has been studied more extensively than phenelzine in antidepressant-resistant depression we consider it first choice in so-called Stage 3 refractory depression.

Phenelzine appears to be a useful alternative, especially if side-effects prevent the administration of higher doses of tranylcypromine.

Acknowledgements

This study was supported by a grant from Parnassia. C. Verploegh and J. Veenhoven assisted in study coordination.

References

Amsterdam JD, Berwish NJ (1989). High dose tranylcypromine therapy for refractory depression. *Pharmacopsychiatry* 22:21-25.

Bech P, Kastrup M, Rafaelsen OJ (1986). Mini-compendium of rating scales for states of anxiety depression mania schizophrenia with corresponding DSM-III syndromes. *Acta Psychiatrica Scandinavica*, 326(Suppl):1-37.

Blackwell B (1991). Monoamine oxidase inhibitor interactions with other drugs. *Journal of Clinical Psychopharmacology* 11:55-59.

Fahy T (1993). Side effects of moclobemide in depressed patients refractory to other treatments. *Irish Journal of Psychology and Medicine* 10,:4-27.

McGrath PJ, Stewart JW, Harrison W, Quitkin, FM (1987). Treatment of tricyclic refractory depression with a monoamine oxidase inhibitor antidepressant. *Psychopharmacolgy Bulletin* 23:169-172.

Nolen W (1997). Classical and selective monoamine oxidase inhibitors in the treatment of depression. In: Honig A, van Praag H (eds). *Neurobiological, Psychopathological and Therapeutic Advances.* Chisester: John Wiley & Sons, 385-395.

Nolen WA, Bloemkolk D (2000). Treatment of bipolar depression, a review of the literature and a suggestion for an algorithm. *Neuropsychobiology* 42(Suppl):11-17.

Nolen WA, Haffmans J (1989). Treatment of resistant depression. Review on the efficacy of various biological treatments, specifically in major depression resistant to cyclic antidepressants. *International Clinical Psychopharmacology* 4:217-228.

Nolen WA, Haffmans JPM, Bouvy PF, Duivenvoorden HJ (1993). Monoamine oxydase inhibitors in resistant major depression. A double blind comparison of brofaromine and tranylcypromine in patients resistant to tricyclic antidepressants. *Journal of Affective Disorders* 28:189-197.

Nolen WA, Van de Putte JJ, Dijken WA, Kamp JS (1985). L-5HTP in depression resistant to re-uptake inhibitors. An open comparative study with tranylcypromine. *British Journal of Psychiatry* 147:16-22.

Nolen WA, Van de Putte JJ, Dijken WA, Kamp JS, Blansjaar BA., Kramer HJ, Haffmans J (1988). Treatment strategy in depression. II. MAO inhibitors in depression resistant to cyclic antidepressants: two controlled crossover studies with tranylcypromine versus L-5-hydroxytryptophan and nomifensine. *Acta Psychiatrica Scandinavica* 78:676-683.

Quitkin FM, Stewart JW, McGrath PJ, Tricamo E, Rabkin JG, Ocepek-Welikson K, Nunes E, Harrison W, Klein DF (1993). Columbia atypical depression. A subgroup of depressives with better response to MAOI than to tricyclic antidepressants or placebo. *British Journal of Psychiatry* Suppl 21:30-34.

Roose SP, Glassman AH, Walsh BT, Woodring S (1986). Tricyclic nonresponders: phenomenology and treatment. *American Journal of Psychiatry* 143:345-348.

Spitzer R, Endicot J (1978). *Schedule for Affective Disorders and Schizofrenia (SADS)* (3rd ed). New York: Biometric Research, New York State Psychiatric Institute.

Thase M, Rush A (1995). Chapter 92: Treatment resistant depression. In: Bloom F, Kupfer D (eds). *Psychopharmacology: The Fourth Generation of Progress.* New York: Raven Press.

Thase ME, Frank E, Mallinger AG, Hamer T, Kupfer DJ (1992). Treatment of imipramine-resistant recurrent depression, III: Efficacy of monoamine oxidase inhibitors. *Journal of Clinical Psychiatr,* 53:5-11.

Thase ME, Mallinger AG, McKnight D, Himmelhoch JM (1992). Treatment of imipramine-resistant recurrent depression, IV: A double-blind crossover study of tranylcypromine for anergic bipolar depression. *American Journal of Psychiatry* 149:195-198.

Thase ME, Trivedi MH, Rush AJ (1995). MAOIs in the contemporary treatment of depression. *Neuropsychopharmacology* 12:185-219.

Van den Broek W, Birkenhager T, Mulder P, Bruijn J, Moleman P (2004). A randomized double-blind study comparing imipramine with fluvoxamine in depressed inpatients. *Psychopharmacology, in press.*

Vink J, Nolen W, Verbraak M (1994). Is moclobemide an alternative for tranylcypromine in treatment-resistant depression? *Tijdschrift voor Psychiatrie* 36:639-647.

Volz HP, Faltus F, Magyar I, Moller HJ (1994). Brofaromine in treatment-resistant depressed patients - a comparative trial versus tranylcypromine. *Journal of Affective Disorders* 30:209-217.

5 | Low-dose esmolol bolus reduces seizure duration during electro-convulsive therapy: a double-blind, placebo-controlled trial

British Journal of Anaesthesia 1999; 83: 271-274

W.W. Van den Broek
Albert F.G. Leentjens
Paul G.H. Mulder
Arinardi Kusuma
Jan A. Bruijn

Chapter 5.

Low-dose esmolol bolus reduces seizure duration during electroconvulsive therapy: a double-blind, placebo-controlled trial.

W.W. Van den Broek, Albert F.G. Leentjen, Paul G.H. Mulder, Arinardi Kusuma, Jan A. Bruijn.

Abstract

We have measured the effect of a bolus dose of esmolol 80 mg i.v. on heart rate, and systolic (SAP), diastolic (DAP) and mean arterial pressure (MAP) during electroconvulsive therapy (ECT). We also assessed seizure duration using both the cuff method and two-lead EEG. We studied 20 patients in a double-blind placebo-controlled, within-patient randomized study. No patient was receiving psychotherapeutic drugs or had cardiovascular disease. Esmolol significantly reduced heart rate, SBP and MAP before the stimulus, and also significantly reduced the increase of these variables during the convulsion, compared to placebo. However seizure duration was also significantly reduced, possibly making ECT less effective. The reduction in seizure duration was 5.83 seconds when monitored clinically and 9.9 seconds when measured by the EEG.

Because of the reduction in seizure duration, routine administration of esmolol is not advisable because it may interfere with the efficacy of ECT, but administration of esmolol during ECT could be useful to reduce tachycardia and hypertension in high-risk patients.

Keywords

Brain, electroconvulsive therapy; sympathetic nervous system, esmolol; complications, seizures; cardiovascular system, effects.

Introduction

During electroconvulsive therapy (ECT), tachycardia and an increase in arterial pressure may be dangerous even in patients with no apparent cardiovascular disease (Geft et al., 1982; Knos et al., 1990; Selvin, 1987). A treatment that could reduce this haemodynamic response, without impairing the efficacy of the treatment, would be useful for routine use.

Theoretically, the beta-blocking agent esmolol is suitable for attenuating the cardiovascular response, as it can be administered i.v. and has an extremely short half-life of 9 min. In this study, we have investigated the effect of a low-dose esmolol bolus on heart rate, arterial pressure and seizure duration during ECT in patients without cardiovascular disease.

ECT is widely used and effective treatment for severe depression, especially when alternative methods of treatment have failed. It is generally considered to be a low-risk procedure. ECT is accompanied by a cardiovascular response that can be dangerous in patients with cardiovascular disease. This response consists of an initial parasympathetic and a subsequent sympathetic reaction. During and immediately after administration of the electrical stimulus, a vagal reaction occurs, which may cause a transient sinus bradycardia or, rarely, asystole. In some centres, atropine or glycopyrrolate are given before induction of anaesthesia to attenuate this vagal effect (Selvin, 1987). The vagal reaction is followed by a transient tachycardia and an increase in arterial pressure during the clonic phase of the convulsion (Abrams, 1997; Selvin, 1987). This cardiovascular response may be harmful in patients with cardiovascular disease. Pre-treatment screening and adequate management of cardiovascular risk factors remain the most important methods of preventing cardiovascular complications caused by ECT. In addition, attenuation of the hyperdynamic reaction during ECT can be important in patients with cardiac conduction defects, hypertension, recent myocardial infarction, haemorrhagic stroke, and aortic or cerebral aneurysms (Abrams, 1997).

Methods

The study was performed in Erasmus Medical Centre in Rotterdam, The Netherlands and approved by the Hospital's Ethics Committee. Written informed consent was obtained from all patients.

We studied 22 patients with a major depressive episode, as defined by the DSM-IV criteria (American Psychiatric Association, 1994). Patients were undergoing ECT because they had failed to respond treatment with a tricyclic antidepressant, followed

by adding lithium and a non-reversible MAO-inhibitor. Exclusion criteria were diastolic arterial pressure greater than 100 mmHg, the use of other beta-adrenergic or calcium-channel blocking drugs, second or third degree atrioventricular block, arrhythmia, hypotension, sinus bradycardia, chronic obstructive pulmonary disease, congestive heart failure, and renal or hepatic failure.

Psychotherapeutic drugs were discontinued in all patients at least 7 days before to ECT. This is common practice in the Netherlands. In this study, this gave an additional advantage of eliminating possible interference of psychotherapeutic drugs with the cardiovascular measures during treatment. We aimed to study 20 patients. In all patients the lungs were preoxygenated. I.v. administration of glycopyrrolate (0.004 mg/kg) and alfentanil (0.010-0.015 mg/kg) was followed by etomidate (0.2-0.3 mg/kg), and succinylcholine (0.5-1.0 mg/kg). Either esmolol or placebo was administered i.v. after glycopyrrolate just before the induction of anaesthesia. Seizure duration was recorded both clinically, using the cuff-method, and by a two-channel electroencephalograph (EEG). The cuff-method consists of inflating a blood pressure cuff up to 300 mmHg just above the right knee, before administration of succinylcholine; as there is no muscle block in the right lower leg, the duration of the convulsion can be timed clinically.

Patients were monitored routinely with a five lead electrocardiograph (ECG) and a pulse oximeter. Systolic and diastolic arterial pressure (SAP, DAP), mean arterial pressure (MAP) and heart rate (HR) were monitored continuously using the Datex Capnomac from arrival in the ECT suite until the patient started breathing spontaneously after the convulsion.

Clinical evaluation of depressive symptoms was performed each week using the 17-item Hamilton rating scale for depression (HRSD) (Hamilton, 1960). Response was defined as a reduction of at least 50% on the HRSD.

Patients were treated twice a week. The first two ECT sessions were not part of the study; they were used to determine the most appropriate doses of etomidate and succinylcholine and these doses were not altered during the remainder of the study. In the subsequent six sessions, patients received a bolus injection of either 80 mg esmolol (10 mg/ml; 8 ml) or placebo (8 ml 0.9% NaCl) before induction of anaesthesia. This was done in a double-blind manner using a within-patient randomized block design, consisting of three two-treatment blocks. In every block one treatment session was the experiment and the other the control condition. Thus every patient received esmolol and placebo on three occasions each during these consecutive sessions. Blinded syringes were prepared by the pharmacy after allocation from a random number table.

Esmolol has a wide therapeutic index and a short half-life and can be given as a fixed dose rather than by patient weight (Sintetos et al., 1987). ECT was started with unilateral brief-pulse, constant current stimulation using the Thymatron DGx. The initial dose of the stimulus was based on the age of the patient (Abrams, 1997). If there was no clinical improvement after four sessions, as measured by the HDRS, bifrontotemporal ECT was substituted. In one patient, ECT was started bilaterally because of the severity of the depression and the earlier good response to this mode of treatment.

If the depressive symptoms ceased before the end of the six double-blind sessions, only data already obtained were used for analysis. If a partial therapeutic response was obtained by after the six sessions, ECT was continued for as long as indicated clinically. These sessions were not included in the study.

Differences in haemodynamic variables between the esmolol and placebo sessions were calculated, in addition to a possible carry-over effect, using repeated measures analysis of variance (rmANOVA). All calculations were performed using the Biomedical Computer Programs P-series (BMDP, module 5V) software package. We analyzed the six measurement sessions with respect to time, three of which were placebo and three esmolol treatments. In each session, the outcome variable was measured twice: immediately before and immediately after the stimulus; a baseline measurement of the outcome variable was obtained one hour before treatment. In the rmANOVA, the explanatory factors were: time (six levels) and random (two levels), with the baseline measurement in each session taken as covariate. Statistical significance was defined as $P < 0.05$.

Results

The number of patients enrolled initially was 22; two patients were excluded one because of bradycardia and asystole in the first two sessions (without study medication) and the second, a 76-year-old man, because he failed to convulse during the first two sessions and required theophylline to facilitate seizures(Leentjens et al., 1996).

Of the 20 patients studied, mean age was 52.7 (range 31-86) yr and mean weight was 63.7 (range 48.4-87.1) kg. Five patients recovered before the end of the study. Eleven patients were changed to bilateral ECT during the study.

At the end of the study, 10 of the participating patients fulfilled the criteria for a good response, showing at least a 50% reduction on the HRDS. This outcome is comparable with other ECT outcome studies in medication-resistant depressed

patients (Prudic et al., 1996; Prudic et al., 1990). There were no significant differences in baseline measures of HR, SAP, DAP, MAP between experiment and control sessions.

Cardiovascular variables measured before and after the stimulus were compared with baseline measurements recorded one hour before treatment (table 1-3). Immediately before the stimulus, HR, SAP and MAP values were significantly less after esmolol than after placebo (table 2).

Table 1. Baseline variables recorded one hour before treatment for experimental and control sessions (mean (SD)). No significant differences.

Variable	Control Mean, (Sd)	Experiment mean, (Sd)	Paired t-test (t)	p-value
Heart rate (beats/minute)	78.8, (11.1)	79.2, (11.5)	t(18)=0.122	0.904
Systolic blood pressure (mmHg)	113.5, (12.3)	113.0, (12.2)	t(18)=0.31	0.976
Diastolic blood pressure (mmHg)	72.4, (11.2)	74.5, (11.2)	t(18)=-1.835	0.083
Mean arterial pressure (mmHg)	86.0, (11.1)	87.3, (11.0)	t(18)=-1.223	0.237

Table 2. Effect of esmolol compared with placebo on variables measured immediately before the stimulus (rmANOVA); control and experimental values are the mean of all patients of each patient's averages of three measurements.

Variable	Control	Experiment	Effect	SEM	p- value
Heart rate (beats/minute)	86.8	80.4	-6.6	1.40	<0.001
Systolic blood pressure (mmHg)	127.6	123.8	-3.8	1.38	0.005
Diastolic blood pressure (mmHg)	78.5	76.4	-1.4	0.97	0.158
Mean arterial pressure (mmHg)	94.8	92.2	-2.3	1.02	0.025

The increase in HR, SAP and MAP after the stimulus was all significantly less after esmolol (table 3). The increase in DAP did not differ significantly between the esmolol and placebo sessions. No significant carry-over effect was found for any of the measured variables, as was expected because of the short half-life of esmolol.

Table 3. Effect of esmolol compared with placebo on variables measured immediately after the stimulus (rmANOVA); control and experimental values are the mean of all patients of each patient's averages of three measurements.

Variables	Control	Experiment	Effect	SEM	p-value
Heart rate (beats/minute)	98.4	86.3	-9.0	1.35	<0.001
Systolic blood pressure (mmHg)	157.6	142.9	-9.4	1.36	<0.001
Diastolic blood pressure (mmHg)	93.8	88.8	-1.7	1.27	0.148
Mean arterial pressure (mmHg)	115.1	106.8	-3.1	1.03	0.002

Doses of etomidate, succinylcholine, alfentanil and glycopyrrolate did not differ significantly over the total course of ECT treatment, as calculated using rmANOVA. This test revealed mean constant doses of 16.0 mg etomidate (chi-square (7=3.46; p=0.840), succinylcholine 68.1 mg (chi-square (7) =3.46; p=0.840), alfentanil 0.91 mg (chi-square (7) =6.75; p=0.455) and glycopyrrolate 0.33 mg (chi-square (7) =10.58; p=0.158).

There was no significant difference in age-based dose of the stimulus between the esmolol and the placebo sessions (p=0.678). Esmolol significantly reduced seizure duration, as measured with the cuff-method and also using the EEG. Clinically, seizure duration was 5.83 seconds (SEM=1.71s; p=0.0007) shorter after esmolol. Seizure duration as measured by the EEG, was reduced significantly by 9.9 seconds (SEM=3.20s; p=0.002) after esmolol compared with placebo.

To obtain an impression of mean seizure duration, we calculated the mean in all patients of a within-patient average of the greatest three measurements (table 4). These calculated averages gave a good impression of the mean; proper estimates of the mean differences can only be obtained from MANOVA.

There were no adverse events that could be attributed to esmolol.

Discussion

We have assessed the effects of a single i.v. of esmolol 80 mg before anaesthesia on cardiovascular response and seizure duration during ECT. Using a double-blind, placebo-controlled, randomized block design and standard anaesthetic and ECT procedures, we attempted to overcome the methodological flaws of some earlier studies in the field. In our study, anaesthesia was not changed after the first two

sessions; concomitant medication remained unchanged for every patient during the study. In other studies, the ECT procedure (dosage and stimulus characteristics) were not specified (Howie et al., 1990; Howie et al., 1992; Kovac et al., 1990). We used an age-based method to determine the initial stimulus and adjusted the dose according to seizure length. Kovac and colleagues used a single dosage for all patients, but did not report the dose (Kovaca et al., 1991). In general, fixed high-dose ECT is recommended only for unilateral ECT. For bilateral ECT, the dose should be 1.5 times threshold. The Thymatron DGx is designed to deliver a stimulus dose that is approximately 2.5 times the seizure threshold with unilateral electrode placement when using the age-based dose method (Sackeim et al., 1993).

Our patients were comparable in age and weight to those in other studies (Howie et al., 1990; Howie et al., 1992; Kovac et al., 1990; Kovac et al., 1991). The response of a 50% remission rate would be expected in medication-resistant patients with a major depression (Prudic et al., 1996).

Esmolol significantly reduced pre-stimulus values of HR, SAP, MAP and the increase in HR, SAP and MAP during the convulsion. Attenuation of the cardiovascular response is brought about by two effects: reduction of baseline values of haemodynamic variables and a reduction in their increase during the convulsion. However, the reduction in the increase in the cardiovascular variables during the convulsion was less than reported in other studies. These studies all used higher esmolol doses, so it is likely that the effect on haemodynamic variables was dose-dependent. This supports the findings of the study of Kovac and colleagues, who compared the effects of two esmolol bolus doses (Kovac et al., 1991). Attenuation of haemodynamic response during ECT can be used to protect patients at risk of cardiovascular complications.

Unfortunately, in addition to attenuating the haemodynamic response, esmolol also significantly reduced seizure duration; confirming findings from earlier studies with esmolol (Howie et al., 1990). It is not clear if this effect is dose-related. The study by Kovac and colleagues is the only one that compared two bolus doses of esmolol; both 100 and 200 mg bolus doses significantly reduced seizure duration, but the extent was not significantly different between doses (Kovac et al., 1991).

Seizure duration is one of the variables used to assess the adequacy of convulsions, and reduction in seizure duration may interfere with therapeutic efficacy. Seizure duration as measured with the cuff method should be at least 25 seconds (Abrams, 1997). However, the relation between therapeutic efficacy and seizure characteristics has recently proved to be more complicated than originally thought. In unilateral ECT, electrical dosages far higher than seizure threshold were

thought to determine efficacy (Sackeim et al., 1993). With bilateral electrode placement, seizure duration is related to efficacy. High electrical dosage related to seizure threshold with bilateral placement causes more severe cognitive side-effects (Sackeim et al., 1993). Generally, it has become clear that neurophysiologic characteristics other than seizure duration are important for seizure quality, such as amplitude, symmetry, coherence and postictal suppression. It is not known as yet how esmolol influences these characteristics and further research is warranted.

In summary, an i.v. bolus dose of esmolol 80 mg, administered immediately before anaesthesia, reduced significantly pre-stimulus HR, SAP and MAP and the increase in HR, SAP and MAP during the convulsion.

However, esmolol also significantly reduced seizure duration. While esmolol can be useful in attenuating haemodynamic response in patients at risk of cardiovascular complications, its effect in reducing seizure duration may interfere with the efficacy of ECT. For this reason its use as a routine prophylactic measure is not advised.

Acknowledgement

We thank Mrs. S. Verploegh for valuable assistance in data collection and other administrative work and Laraine Visser-Isles (Erasmus University) for English language editing.

References

Abrams R (1997). *Electroconvulsive Therapy* (3rd ed). New York Oxford: Oxford University Press.

American Psychiatric Association (1994). *Diagnostic and statistical manual of mental disorders* (4th ed). Washington DC: American Psychiatric Association.

Geft IL, Fishbein MC, Ninomiya K, Hashida J, Chaux E, Yano JJYR, Genov T, Shell W, Ganz W (1982). Intermittent brief periods of ischemia have a cumulative effect and may cause myocardial necrosis. *Circulation* 66:1150-1153.

Hamilton M (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry* 23:56-61.

Howie MB, Black HA, Zvara D, McSweeney TD, Martin DJ, Coffman JA (1990). Esmolol reduces autonomic hypersensitivity and length of seizures induced by electroconvulsive therapy. *Anesthesia Analgesia* 71:384-388.

Howie MB, Hiestand DC, Zvara DA, Kim PY, McSweeney TD, Coffman JA (1992). Defining the dose range for esmolol used in electroconvulsive therapy hemodynamic attenuation. *Anesthesia Analgesia* 75:805-810.

Knos GB, Sung YF, Cooper RC, Stoudemire A (1990). Electroconvulsive therapy-induced hemodynamic changes unmask unsuspected coronary artery disease. *Journal of Clinical Anesthesiology* 2:37-41.

Kovac AL, Goto H, Arakawa K, Pardo MP (1990). Esmolol bolus and infusion attenuates increases in blood pressure and heart rate during electroconvulsive therapy. *Canadian Journal of Anaesthesiology* 37:58-62.

Kovac AL, Goto H, Pardo MP, Arakawa K (1991). Comparison of two esmolol bolus doses on the haemodynamic response and seizure duration during electroconvulsive therapy. *Canadian Journal of Anaesthesiology* 38:204-209.

Leentjens AF, Van den Broek WW, Kusuma A, Bruijn JA (1996). Facilitation of ECT by intravenous administration of theophylline. *Convulsive Therapy* 12:232-237.

Prudic J, Haskett RF, Mulsant B, Malone KM, Pettinati HM, Stephens S, Greenberg R, Rifas SL, Sackeim HA (1996). Resistance to antidepressant medications and short-term clinical response to ECT. *American Journal of Psychiatry* 153:985-992.

Prudic J, Sackeim H, Devanand D (1990). Medication resistance and clinical response to electroconvulsive therapy. *Psychiatry Research* 31:287-296.

Sackeim HA, Prudic J, Devanand DP, Kiersky JE, Fitzsimons L, Moody BJ, McElhiney MC, Coleman EA, Settembrino JM (1993). Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy [see comments]. *New England Journal of Medicine* 328:839-846.

Selvin BL (1987). Electroconvulsive therapy-1987. *Anesthesiology* 67:367-385.

Sintetos AL, Hulse J, Pritchett EL (1987). Pharmacokinetics and pharmacodynamics of esmolol administered as an intravenous bolus. *Clinical Pharmacology Therapy* 41:112-117.

6 Double-blind placebo controlled study to the effects of etomidate-alfentanil anesthesia in electro-convulsive therapy

In press, Journal of ECT, 2004

Walter W. van den Broek
Theo H.N. Groenland
Arinardi Kusuma
Paul G.H. Mulder
Jan A. Bruijn

Chapter 6.

Double-blind placebo controlled study to the effects of etomidate-alfentanil anesthesia in electroconvulsive therapy

Walter W. van den Broek, Theo H.N. Groenland, Arinardi Kusuma, Paul G.H. Mulder, Jan A. Bruijn

Abstract

The effect of etomidate and alfentanil on heart rate (HR), systolic arterial pressure (SAP), diastolic arterial pressure (DAP) and mean arterial pressure (MAP) was compared with etomidate and placebo during electroconvulsive therapy (ECT). We also studied the influence of alfentanil on seizure duration using both the cuff method and two lead electroencephalographs (EEG), on the prevention of myoclonus induction by etomidate, on duration of apnea and on postictal agitation after ECT. We enrolled 21 consecutive patients in a prospective placebo-controlled, within patient blocked randomized study. Alfentanil significantly reduced HR, DAP and MAP both before and after the stimulus. The increase in these variables during the convulsion was not affected, compared with placebo. Alfentanil had no effect on seizure duration. However, apnea duration was prolonged during the alfentanil sessions as compared with placebo (73 seconds). Alfentanil did not significantly reduce the occurrence of myoclonus after etomidate as compared with placebo, nor did postictal agitation after ECT appear more often with alfentanil.

Alfentanil could be useful to reduce tachycardia and hypertension during ECT in high risk patients without effects on seizure duration. Alfentanil itself has no proconvulsive effect in combination with etomidate

Keywords

Electroconvulsive therapy, cardiovascular system, alfentanil, etomidate, seizures, complications, brain, apnea, myoclonus.

Introduction

The antidepressant effect of ECT is mainly dependent on the generalized seizure induced. The precise relationship between seizure characteristics and clinical effects is unknown. The efficacy of ECT relates to seizure duration and to the relative stimulus dosage above seizure threshold (Sackeim et al., 1993).

ECT is often the first line of treatment for the elderly. Adequate seizures may be difficult to achieve in patients with advanced age. Other factors diminishing elicitation of seizures are: somatic co morbidity and repeated seizure induction (Coffey et al., 1995). Effective techniques to overcome failure to convulse or inadequate seizures include greater stimulus intensity, hyperventilation, pre-treatment with caffeine or theophylline, or etomidate-induced anesthesia. Etomidate is a short-acting nonbarbiturate imidazole derivative, with rapid onset, that is rapidly metabolized. It has no analgesic properties and minimal cardio respiratory effects (Wauquier, 1983). Seizure duration was found to be longer with etomidate than methohexital and propofol (Avramov et al., 1995). Etomidate is reported to be associated with longer seizure duration than thiopentone (Christensen et al., 1986; Trzepacz et al., 1993). Etomidate can be the anesthetic of choice especially with elderly patients who have higher seizure thresholds than younger patients. If patients remain refractory to stimulus elicitation pre-treatment with caffeine or theophylline is an option (Leentjens et al., 1996). There could be a risk of cardiovascular dysfunction after pre-treatment with caffeine or theophylline. Since its minimal cardiovascular effects etomidate may be preferred as anesthetic in such circumstances.

Patients may experience myoclonus due to anesthesia induction with etomidate. Pain at the injection site is prevented with the use of etomidate lipid emulsion.

Alfentanil is a rapid-acting opioid with an ultra short duration of action. Positive effects on seizure duration are reported in combination with methohexitone and propofol. Alfentanil used to reduce the dose of propofol or methohexitone resulted in longer seizure duration (Nguyen et al., 1997).

In this study we compared the use of etomidate with alfentanil and etomidate with placebo.

We were interested in the effect of alfentanil compared to placebo with standard etomidate anesthesia on seizure duration. In addition, we investigated the effect of alfentanil on heart rate and blood pressure. The cardiovascular response during ECT is caused by activation of the autonomic nervous system. Initial parasympathetic activation results in bradycardia that is rapidly followed by sympathetically-induced tachycardia and hypertension. This cardiovascular response may be harmful in

patients with cardiovascular disease. Alfentanil could reduce the stress of the procedure and attenuate the cardiovascular response. With tracheal intubations alfentanil attenuated the cardiovascular and catecholamine response (Miller et al., 1993).

Other aims of this study were to investigate the prevention of myoclonus induction by etomidate, the influence of alfentanil on duration of apnea, and on postictal agitation (marked agitation and restlessness immediately postictal).

Patients and methods

The study was performed on the depression unit of the department of Psychiatry at the Erasmus Medical Centre, a university hospital. The study was approved by the Hospital's Ethics Committee. Written informed consent was obtained from all 21 depressed inpatients included in the study. Most of the patients in the Netherlands undergoing ECT have medication resistant depressive disorder. Exclusion criteria were: known intolerance to opioids and other indications for ECT then depressive disorder.

Psychotropic drugs were discontinued in all patients at least 7 days before ECT; this is common practice in the Netherlands. In the present study, this resulted in an additional advantage of eliminating possible interference with the measures taken during treatment.

In the second and subsequent five ECT sessions patients received intravenous (i.v.) administration of metoclopramide 10 mg, glycopyrrolate 0.002-0.003 mg kg^{-1}, a bolus injection of either alfentanil 0.010-0.015 mg kg^{-1} or placebo (0.9 NaCl) in identical volumes and etomidate 0.2-0.3 mg kg^{-1} followed by succinylcholine 0.5-1.0 mg kg^{-1}. After the second session the dosages of the drugs used were maintained during the ECT treatment course.

The administration of alfentanil or placebo was done in a double-blind cross-over fashion with four sequences of six periods with two treatments. Thus, every patient received at random alternately alfentanil and placebo, both totally on three occasions according to one sequence arbitrarily drawn out of four sequences (Williams, 1949). Blinded syringes were prepared by the pharmacy according to a computer-generated randomization list. In all patients the lungs were preoxygenated. Observation of myoclonic jerks after the administration of etomidate was performed by the psychiatrist and the anesthetist until the succinylcholine was administered. Presence of myoclonic jerks was established if the psychiatrist and the anesthetist both agreed to its occurrence.

The duration of apnea during a treatment session was assessed with a stopwatch from the start of oxygenation until recovery of spontaneous respiration. Postictal agitation after treatment was observed during the recovery period in the recovery by the psychiatrist and nurses and on the psychiatric ward on the day of treatment by the attending psychiatric nurses.

Seizure duration was recorded both clinically using the cuff method, and by a two channel electroencephalograph (EEG). The cuff method consists of inflating a blood pressure cuff above the right knee to 300 mm Hg, before the administration of succinylcholine; because there is no neuromuscular block in the right lower leg, duration of the convulsion can be timed clinically.

One hour before the treatment session a baseline blood pressure and heart rate were recorded.

During the session patients were monitored routinely with a three-lead ECG and a pulse oximeter. Systolic and diastolic arterial pressure (SAP, DAP), mean arterial pressure (MAP) and heart rate (HR) were monitored continuously (using the Datex Capnomac) from arrival in the ECT suite until the patient started breathing spontaneously after the convulsion.

Clinical evaluation of depressive symptoms was performed each week using the 17-item version of the Hamilton rating scale for depression (HRSD). Response was defined as a reduction of at least 50% on the HRSD, and a score of < 10 on the HRSD was defined as remission. Patients were treated twice a week with bifrontotemporal electrode placement. The ECT machine was a brief pulse constant current Thymatron DGx. The first ECT session was not part of the study; this session was used to determine the seizure threshold. This was done with a titration procedure. For patients younger then 50 years of age we used the following titration schedule: 5%, 10%, 20%, 40% and 80%. For patients older then 50 years we used: 10%, 20%, 40% and 80%.

If the starting stimulus dose failed to elicit a seizure of at least 25 seconds duration measured with the cuff method, stimulus charge was increased according to the titration schedule and the patient was restimulated after 30 seconds. Seizure threshold was defined as the stimulus dosage that elicited a seizure of at least 25 seconds according to the cuff method. For the second treatment the stimulus dosage was set at 1.5 times the initial seizure threshold and, during the course of ECT, stimulus dosage settings were adjusted upward in order to maintain seizure duration of at least 25 seconds as measured with the cuff method.

If the depressive symptoms ceased before the end of the six double-blind sessions, only data already obtained were used for analysis. If a partial therapeutic

response was obtained after the six study sessions, ECT was continued as long as was indicated clinically. These sessions were not included in the study, except for the clinical evaluation of the effect on the depressive symptoms.

Differences in hemodynamic variables between the alfentanil and placebo sessions were estimated and tested using mixed model analysis of variance (ANOVA). We analyzed the six measurements in time as repeated measurements, three of which were taken under placebo and three under alfentanil treatment. In each session the outcome variable was measured twice: immediately before and immediately after the stimulus; a baseline measurement of the outcome variable in each session was obtained 1 hour before treatment. In the mixed model ANOVA, the explanatory factors were time (six levels) and random (two levels), with the baseline measurement in each session taken as covariate.

Differences in seizure and apnea duration between the alfentanil and placebo sessions were also estimated and tested using mixed model ANOVA. The from session to session correlation structure was assumed to be first order autoregressive.

Comparison for the occurrence of myoclonus and postictal agitational state between the placebo and alfentanil sessions were made with the Wilcoxon signed rank test after averaging the scores over the three placebo and over the three alfentanil sessions. All calculations were performed using SAS software version 6.12. Statistical significance was defined as $P< 0.05$.

Results

We studied 21 patients, 15 female and 6 male with a mean age 53±11.72 (range 29-79) years and mean weight 65.7 kg ± 13.9 (range 40-96) kg. Six patients recovered before the end of the study. One patient needed only two sessions. Fourteen (66.7%) patients fulfilled the criteria for a good response, showing at least a 50% reduction on the HRSD. Nine (42.9%) of the 21 patients were completely recovered as defined by an HRSD of < 10. There were no significant differences in baseline measures of HR, SAP, DAP and MAP between control and experimental sessions.

Preliminary results for the cardiovascular variables and apnea duration of the whole sample are accepted as letter to the editor of the Canadian Journal of Anesthesiology.

Cardiovascular variables measured before and after the stimulus, were compared with baseline measurements recorded one hour before treatment. Immediately before and after the stimulus the means of DAP, HR and MAP were significantly

smaller after alfentanil than after placebo (Table 1). Mean SAP was not significantly smaller after placebo before and after the stimulus.

Table 1. Effect of alfentanil compared with placebo on variables measured before and after the ECT stimulus; placebo and alfentanil values are baseline-adjusted means estimated over three periods using mixed model ANOVA. SE= standard error.

Before the stimulus

Variable	Placebo	Alfentanil	Effect	SE of effect	P
Heart rate (beat min $^{-1}$)	89.5	85.2	-4.29	1.43	0.0036
Systolic arterial pressure (mmHg)	131.1	127.9	-3.15	1.70	0.0665
Diastolic arterial pressure (mmHg)	80.6	76.9	-3.70	1.15	0.0019
Mean arterial pressure (mmHg)	97.5	93.9	-3.67	1.26	0.0046

After the stimulus

Variable	Placebo	Alfentanil	Effect	SE of effect	P
Heart rate (beat min $^{-1}$)	103.6	95.5	-8.08	2.42	0.0013
Systolic arterial pressure (mmHg)	156.2	151.2	-5.04	2.45	0.0428
Diastolic arterial pressure (mmHg)	91.1	87.0	-4.13	1.63	0.0134
Mean arterial pressure (mmHg)	112.8	108.3	-4.48	1.85	0.0176

The mean increments from before to after the stimulus were not significantly different between alfentanil and placebo sessions for all the cardiovascular variables (HR, SAP, DAP, MAP). The above results were adjusted for baseline. Additionally adjusting for period, gender and age in the mixed model ANOVA produced the same results.

There was no significant difference in mean seizure duration as measured with

EEG between alfentanil and placebo sessions as calculated with mixed model ANOVA (placebo = 86 seconds, alfentanil = 80 seconds, standard error of the mean (SEM) difference= 7.1, p= 0.406). Analysis with mixed model ANOVA adjusted for gender, age, dosage and period showed a significant period effect with a reduction of 4.35 seconds (SE=1.89, p= 0.024) for each consecutive period and a significant effect of age, an increase of one year in age results in a decrease of seizure duration of 1.06 seconds (SE=0.27, p= 0.0009).

The difference in mean apnea duration (as calculated with mixed model ANOVA) between the alfentanil and placebo sessions was significant, the alfentanil sessions were on average 73 seconds longer (SE= 17.5, p= 0.0001). There were no significant differences between the placebo and alfentanil sessions for the appearance of postictal agitational state, and the occurrence of myoclonus after etomidate administration (Wilcoxon signed rank test).

Discussion

Alfentanil significantly reduced pre-stimulus values of HR, DAP and MAP. After the stimulus HR, DAB and MAP were still significantly lower in the alfentanil sessions than after placebo. The difference in the values after and before the stimulus was not significantly different between the alfentanil and placebo sessions.

Mean seizure duration was not significantly different between placebo and alfentanil sessions, apnea duration was significantly longer in alfentanil sessions. There were no significant differences in the occurrence of myoclonus and postictal agitational state between placebo and alfentanil sessions.

Alfentanil may lower HR, DAP and MAP due to reduction of catecholamine release both before and after the stimulus. The effect of alfentanil before the stimulus may be caused by its attenuating effect on the stress response and catecholamine release due to the ECT procedure.

In comparable dosage (0.015 mg kg^{-1}) alfentanil reduced SAP, HR response and catecholamine concentration in plasma to tracheal intubations following induction of anesthesia with thiopentone. In a dosage of 0.030 mg kg^{-1} alfentanil the catecholamine stress response to tracheal intubations was completely suppressed (Miller et al., 1993).

The tachycardia and rise of blood pressure during ECT is preceded during and immediately after the electrical stimulus by a sharp vagal parasympathetic outflow that is both neurally mediated and consequent to a Valsalva effect induced by forced

expiration against a closed glottis. The fact that periods of bradycardia and asystole can occur in sub convulsive stimuli demonstrates that the electrical stimulus, rather than the induced seizure is responsible for this vagal effect (Wells et al., 1988).

A sympathoadrenal tachycardia then supervenes in case of a seizure. This is initially driven by direct sympathetic neural outflow of discharging cardio accelerator areas in the hypothalamus (Welch and Drop, 1989).

Adrenal medullar catecholamine release later in the seizure may contribute to maintaining heart rate above baseline (Cuche et al., 1990).

No effect on SAP was found in this trial. Since the catecholamine effect after the stimulus is elicited by the seizure, the attenuating affect of alfentanil before the stimulus can only be contributed to an attenuating effect of the catecholamine release due to the stress of the procedure. Higher dosage of alfentanil could eventually attenuate the SAP at the cost of longer apnea duration. In less comparable procedures: before cardiac and abdominal surgery and with a much higher dosage of alfentanil, etomidate and alfentanil showed a greater decrease in MAP than a combination of etomidate and fentanyl (Spiss et al., 1984), and improvement of myocardial oxygen demand (Rucquoi and Camu, 1983).

Alfentanil does not lengthen seizure duration compared to placebo. This is in contrast to the findings of Nguyen and colleagues who found that the combination of methohexitone and alfentanil resulted in longer seizure duration compared to methohexital alone, propofol with alfentanil and propofol alone (Nguyen et al., 1997).

Clearly, in this latter study, this effect can be accounted for by the reduced dosage of methohexital and propofol when used in combination with alfentanil. Alfentanil itself does not lengthen seizure duration in combination with etomidate. Even after analysis with mixed model ANOVA adjusted for gender, age, dosage and period no significant difference could be found. Two variables showed to be important predictors for seizure duration: period and age showed a significant effect in this analysis. We did not have to adjust the analysis for electrode placement, an important variable influencing seizure duration, because all patients were treated with bifrontotemporal electrode placement.

Etomidate causes myoclonic movements during induction of anesthesia. Alfentanil pretreatment did not influence the appearance of myoclonus compared to the placebo sessions. We have the clinical impression that some patients are more susceptible to this side effect, during the course of treatment habituation to this side effect seems to appear. Methohexital also has excitatory effects during the induction

of anesthesia. Patients undergoing a short anesthesia with methohexital for placing a retrobulbar block before cataract extraction had significantly less myoclonus when pretreated with alfentanil (0.005 mg kg_{-1}) compared to lidocaine and placebo (Khalil et al., 1998).

In our study alfentanil did not reduce the appearance of myoclonus compared to placebo. In our study the incidence of myoclonus could have been to low to show a significant difference between alfentanil and placebo.

All patients have some degree of confusion and disorientation immediately following ECT. Initial disorientation and confusion generally subsides within 10-20 minutes and typically is resolved within one hour. Approximately 10% of patients will develop marked agitation and restlessness immediately postictal. We observed that patients showing marked agitation and restlessness after treatment sometimes needed interventions such as i.v. administration of a short acting, rapid-onset benzodiazepine: midazolam. There was no significant difference in the appearance of marked agitation and restlessness after the alfentanil sessions compared with the placebo sessions, as analyzed with the Wilcoxon signed rank test.

Acknowledgements

We thank Mrs. S. Verploegh for valuable assistance in data collection and other administrative work, and Laraine Visser-Isles (Erasmus University Rotterdam) for English language editing.

References

Avramov MN, Husain MM, White PF (1995). The comparative effects of methohexital, propofol, and etomidate for electroconvulsive therapy. *Anesthesia Analgesia* 81:96-602.

Christensen P, Kragh-Sorensen P, Sorensen C, Thomsen HY, Iversen AD, Christensen KS, Huttel M, Tonnesen E (1986). EEG-Monitored ECT: A Comparison of Seizure Duration under Anesthesia with Etomidate and Thiopentone. *Convulsive Therapy* 2:145-150.

Coffey CE, Lucke J, Weiner RD, Krystal AD, Aque M (1995). Seizure threshold in electroconvulsive therapy: I. Initial seizure threshold. *Biological Psychiatry* 37:713-720.

Cuche JL, Brochier P, Klioua N, Poirier MF, Cuche H, Benmiloud M, Loo H, Safar M (1990). Conjugated catecholamines in human plasma: where are they coming from? *Journal of Laboratory and Clinical Medicine* 116:681-686.

Khalil SN, Howard G, Mankarious R, Campos C, Kellaway J, Chuang AZ, Ruiz R. (1998). Alfentanil decreases the excitatory phenomena of sodium methohexital. *Journal of Clinical Anesthesiology* 10:469-473.

Leentjens AF, Van den Broek WW, Kusuma A, Bruijn JA (1996). Facilitation of ECT by intravenous administration of theophylline. *Convulsive Therapy* 12:232-237.

Miller DR, Martineau RJ, O'Brien H, Hull KA, Oliveras L, Hindmarsh T, Greenway D (1993). Effects of alfentanil on the hemodynamic and catecholamine response to tracheal intubation. *Anesthesia Analgesia* 76:1040-1046.

Nguyen TT, Chhibber AK, Lustik SJ, Kolano JW, Dillon PJ, Guttmacher LB (1997). Effect of methohexitone and propofol with or without alfentanil on seizure duration and recovery in electroconvulsive therapy. *British Journal of Anaesthesiology* 79:801-803.

Rucquoi M, Camu F (1983). Cardiovascular responses to large doses of alfentanil and fentanyl. *British Journal of Anaesthesiology* 55 (Suppl 2): 223S-230S.

Sackeim HA, Prudic J, Devanand DP, Kiersky JE, Fitzsimons L, Moody BJ, McElhiney MC, Coleman EA, Settembrino JM (1993). Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy [see comments]. *New England Journal of Medicine* 328:839-846.

Spiss CK, Coraim F, Haider W, White PF (1984). Haemodynamic effects of fentanyl or alfentanil as adjuvants to etomidate for induction of anaesthesia in cardiac patients. *Acta Anaesthesiologica Scandinavica* 28:554-556.

Trzepacz PT, Weniger FC, Greenhouse J (1993). Etomidate anesthesia increases seizure duration during ECT. A retrospective study. *General Hospital Psychiatry* 15:115-120.

Wauquier A (1983). Profile of etomidate. A hypnotic, anticonvulsant and brain protective compound. *Anaesthesia* 38 (Suppl):26-33.

Welch CA, Drop LJ (1989). Cardiovascular Effects of ECT. *Convulsive Therapy* 5:35-43.

Wells DG, Zelcer J, Treadrae C (1988). ECT-induced asystole from a sub-convulsive shock. *Anaesthesiology Intensive Care* 16:368-371.

Williams E (1949). Experimental designs balanced for the estimation of residual effects of treatments. *Australian Journal of Scientific Research* 2:149-168.

7 | ECT response in delusional versus non-delusional depressed inpatients

Journal of Affective Disorders 2003; 74: 191-195.

Tom K. Birkenhäger
Esther M. Pluijms
Stefan A. P. Lucius

Chapter 7.

ECT response in delusional versus non-delusional depressed inpatients

Tom K. Birkenhäger, Esther M. Pluijms, Stefan A. P. Lucius

Abstract

Background

ECT is often considered more effective in delusional than in non-delusional depressives, although the literature does not support this view.

Methods

We reviewed the records of 55 consecutive inpatients with major depression according to the DSM-III-R criteria and distinguished two subtypes: patients with delusions and those without. We examined whether the deluded patients showed a higher response rate.

Results

Using 50% reduction on the Hamilton Rating Scale for Depression (HRSD) as response criterion, the efficacy of ECT was higher in patients with delusional depression (92% response) than in the non-deluded patients (55% response). Considering a post-ECT HRSD score of ≤ 7 as remission criterion, patients with delusions again showed a higher remission rate (57% versus 24%).

Limitations

This study has a retrospective nature and a rather homogenous sample.

Conclusion

ECT appears to be an effective treatment for severely depressed inpatients, both with and without delusions. The efficacy of ECT was superior in patients with delusional depression, considering the number of patients achieving partial remission as well as full remission.

Keywords

Major depression; delusional depression; psychotic depression; electroconvulsive therapy

Introduction

Electroconvulsive therapy (ECT) is considered to be the most effective treatment for major depression (Abrams, 1997). In many countries, ECT is still considered an exceptional treatment, administered to severely depressed patients only.

The presence of delusions has been considered a useful predictor of a favorable response to ECT, but the more recent literature is divided on this point. Some studies report a superior response in delusional than in non-delusional depressives (Avery and Lubrano, 1979; Buchan et al., 1992) and others fail to find a difference (Kindler et al., 1991; O'Leary et al., 1995; Rich et al., 1986; Sobin et al., 1996; Solan et al., 1988). Most studies show methodological flaws (see O'Leary et al., 1995), with the studies of Kindler et al. (1991) and Sobin et al. (1996) being considered the most valuable.

The results of the above studies may not be applicable to the population of depressed patients receiving ECT in the Netherlands, where ECT is an exceptional treatment. The present study retrospectively examines the relation between the presence or absence of delusions and the efficacy of ECT in a population of severely depressed inpatients, most of them being medication resistant.

Methods

Patient selection

We reviewed the records of 55 inpatients who met the DSM-III-R (American Psychiatric Association, 1987) criteria for major depression. Diagnoses were based on clinical observation. A diagnosis of delusional depression was made only when the patient had expressed, either spontaneously or on inquiry, definite mood-congruent delusions. When the case notes of an individual patient left any room for doubt about the presence of delusions, the patient was included in the non-psychotic group.

All patients were treated consecutively with ECT between December 1993 and December 2000 at the Department of Biological Psychiatry of Parnassia Psychomedical Center, The Hague, The Netherlands. This department is almost exclusively reserved for patients suffering from severe resistant depression.

Patients receiving ECT were either medication resistant or in a critical condition (mutistic, refusing food). We restricted our sample to patients who were free from neurologic or serious medical illness and who had never been treated with ECT previously.

If patients received more than one course of ECT during the study period, only the first course of ECT was reviewed.

Electroconvulsive therapy

Nineteen patients received right unilateral (d' Elia) ECT only, another 19 patients initially received right unilateral ECT and were crossed over to bilateral ECT, because of insufficient response after three to 11 treatments, and 17 patients received bilateral ECT from the start, because of the severity of the illness based on clinical observation (see Table 3). ECT was administered with a brief-pulse, constant-current apparatus (Thymatron, Somatics, Lake Bluff, IL, USA) under thiopental anesthesia (1.0–2.5 mg/kg) and succinylcholine (1.0 mg/kg) for muscle relaxation. Patients were oxygenated (100% oxygen, positive pressure) until the resumption of spontaneous respiration. Physiological monitoring included pulse oximetry, electrocardiogram (ECG) and electroencephalogram (EEG). ECT was administered at a schedule of two treatments per week with moderate-to-high stimulus intensity (288–504 millicoulomb), without measuring seizure threshold by empirical stimulus titration. The number of ECT treatments was determined by clinical observation, and a minimum of 10 bilateral treatments was required before evaluation as a non-responder. ECT was continued until patients were either asymptomatic or had not shown further improvement over three consecutive treatments. Patients were withdrawn from all psychotropic medication at least 1 week before ECT and were maintained medication free during the course of ECT in all but seven cases. Those patients received 5 mg droperidol prior to ECT for severe anxiety. Three of them also received haloperidol 1–3 mg daily to control severe agitation.

Evaluation of treatment outcome

The presence of delusions and each patient's strongest antidepressant medication trial prior to ECT were evaluated independently and rated by a psychiatrist (T.K.B.) and a resident (E.M.P.) using the Antidepressant Treatment History Form (ATHF) (Keller et al., 1986; Sackeim et al., 1990). Patients scoring 3 or more on this 0–5 scale are classified as medication resistant. Scores on the 17-item Hamilton Rating Scale for Depression (HRSD) (Bech et al., 1986) were routinely recorded in the patients' case notes prior to ECT, during ECT and following treatment termination. These HRSD scores were used in two different ways for classification of the response to ECT: a reduction in HRSD score of at least 50% post-treatment compared to pre-treatment and a post-treatment HRSD score of ≤ 7 in patients considered in full remission.

Chi-square tests were used to analyze the differences in response rate between patients with delusional depression and the non-deluded patients. Student's two-tailed t-tests were used to compare group means. Statistical analyses were performed using SPSS for Windows (version 9.0).

Results

The total patient sample consisted of 55 inpatients, 40 women and 15 men, with a mean age of 50.4 years (range 20–70 years). Twenty-six patients suffered from delusional depression and 29 from depression without delusions. Table 1 shows the demographic and clinical characteristics for the total sample and as a function of either the presence or absence of delusions. The mean age was higher in the deluded group (54.9 versus 46.4 years; P=0.003). Forty-one patients were classified as medication resistant while the remaining 14 patients had received inadequate treatment with antidepressants prior to ECT. Both the deluded and the non-deluded sample contained the same proportion of patients with established medication resistance. This is a relevant finding, because resistance to antidepressant pharmacotherapy may result in a reduced response rate to ECT (Prudic et al., 1990).

Table 1. Demographic and clinical characteristics

Variable	Total sample (N=55)	Depressed patients with delusions (N=26)	Depressed patients without delusions (N=29)
Age in years, mean (S.D.)	50.4 (10.7)	54.9 (9.5)	46.4 (10.3)
Female sex, N (%)	40 (72.7)	18 (69.2)	22 (75.9)
Medication resistant[a], N (%)	41 (74.5)	19 (73.1)	22 (75.9)
Length of index episode in Months, mean (S.D.)	23.1 (18.9)	16.1 (13.6)	29.4 (20.9)
No of previous depressive Episodes,mean (range)	1.6 (0-6)	2.0 (0-6)	1.2 (0-5)

[a] Patients were classified as medication resistant according to the ATHF (Antidepressant History Form) when their rating on this scale was 3 or more (Sackeim et al., 1990)

Patients without delusions had a significantly longer mean duration of their current depressive episode than the deluded patients (29.4 versus 16.1 months; P=0.008), which may well have influenced the results to the disadvantage of the non-deluded group. The mean number of ECT treatments for patients achieving full remission for patients with and without delusions was 10.4 (range 4–18) and 13.7 (range 7–25), respectively. The mean number of ECTs for patients who failed to achieve full remission was 16.7 (range 10–24) in the deluded sample and 16.9 (range 10–27) in patients without delusions.

Table 2 shows the HRSD scores prior to ECT and following treatment termination for the total sample and as a function of either the presence or absence of delusions. Both groups show no significant difference in HRSD scores prior to ECT. Twenty-four of the 26 (92%) patients with delusional depression and 16 of the 29 (55%) non-deluded patients responded to ECT according to the response criterion of 50% reduction of the HRSD score. This difference in response rate is statistically significant ($\chi 2=12.1$; P=0.002).

Table 2. Pre- and post-ECT scores on the HRSD and number of responders to ECT

Variable	Total sample (N=55)	Depressed patients with delusions (N=26)	Depressed patients without delusions (N=29)	P-value
Pre-ECT HRSD score, Mean (S.D.)	26.6 (5.4)	28.2 (5.9)	25.1 (4.5)	0.035
Post-ECT HRSD Score, mean (S.D.)	10.3 (5.3)	8.4 (3.7)	12.0 (5.9)	0.009
HRSD score≤ 7	41 (74.5)	24 (92.3)	16 (55.1)	0.002
Post-ECT,N (%)	22 (40.0)	15 (57.6)	7 (24.1)	0.01

Using a HRSD score of ≤ 7 (full remission) as response criterion, 15 of the 26 (58%) deluded patients and seven of the 29 (24%) patients without delusions responded to ECT. Again, this difference in response rate is statistically significant ($\chi 2=6.4$; P=0.01) (Table 3).

Table 3. Number of patients achieving full remission as a function of ECT method.

ECT method	Depressed patients With delusions	Depressed patients without delusions	Total sample
Unilateral only (responders/total)	8/12	2/7	10/19
Unilateral switched to bilateral (responders/total)	0/3	2/16	2/19
Bilateral only (responders/total)	7/11	3/6	10/17

Discussion

In our study, the response to ECT was significantly superior in delusional depressed patients than in non-delusional patients. This finding is contradictory to the results of several previous studies. A number of factors may account for this contradiction. The longer duration of the index episode in the non-deluded group in our study is a possible confounding factor. Various aspects of the administration of ECT can also explain the differences in ECT response among studies.

In the present study, ECT was administered after a 1 week washout of psychotropic drugs, without concomitant benzodiazepines, with a relatively high electrical charge, and a flexible number of treatments with the aim of maximal clinical improvement. Only two previous studies provide clear information about concomitant medication and the electrical dose of ECT; both studies also used a relatively high electrical charge (Kindler et al., 1991; Sobin et al., 1996), but in the latter study an unspecified number of patients were allowed to use lorazepam during the course of ECT, which may well have reduced the ECT response (Jha and Stein, 1996). It is conceivable that, in some of the earlier studies, which provide little or no information on the ECT procedure, unilateral ECT at low dosage was administered, which is nowadays considered an ineffective form of ECT (Sackeim et al., 2000). Since delusional depressed patients may show a lower placebo response than non-delusional depressed patients (Schatzberg and Rothschild, 1992), administration of ineffective ECT could reduce the response in delusional patents more than in patients without delusions. The concurrent use of antidepressants in some of the earlier studies might have improved the response in non-delusional patients, but less so in delusional depressed patients.

Differences in patient selection may also account for the different results. In most studies, information about in- or outpatient status is lacking; only in one previous paper is it clearly mentioned that the sample consisted of inpatients (Kindler et al., 1991). In the present study we included only delusional depressed patients with mood-congruent delusions. Except for one study (Sobin et al., 1996), the qualification of mood-congruence with regard to delusions is not mentioned.

In the present study, although ECT was shown to be an effective treatment for depressed patients both with and without delusions, the response of patients with delusions was significantly superior.

References

Abrams R (1997). *Electroconvulsive Therapy* (3rd ed). New York Oxford: Oxford University Press.

Avery D, Lubrano A (1979). Depression treated with imipramine and ECT: the DeCarolis study reconsidered. *American Journal of Psychiatry* 136:559-562.

Bech P, Kastrup M, Rafaelsen OJ (1986). Mini-compendium of rating scales for states of anxiety depression mania schizophrenia with corresponding DSM-III syndromes. *Acta Psychiatrica Scandinavica* 326 (Suppl):1-37.

Buchan H, Johnstone E, McPherson K, Palmer RL, Crow TJ, Brandon S (1992). Who benefits from electroconvulsive therapy? Combined results of the Leicester and Northwick Park trials. *British Journal of Psychiatry* 160:355-359.

Jha A, Stein G (1996). Decreased efficacy of combined benzodiazepines and unilateral ECT in treatment of depression. *Acta Psychiatrica Scandinavica* 94:101-104.

Keller MB, Lavori PW, Klerman GL, Andreasen NC, Endicott J, Coryell W, Fawcett J, Rice JP, Hirschfeld RM (1986). Low levels and lack of predictors of somatotherapy and psychotherapy received by depressed patients. *Archives of General Psychiatry* 43:458-466.

Kindler S, Shapira B, Hadjez J, Abramowitz M, Brom D, Lerer B (1991). Factors Influencing Response to Bilateral Electroconvulsive Therapy in Major Depression. *Convulsive Therapy* 7:245-254.

O'Leary D, Gill D, Gregory S, Shawcross C (1995). Which depressed patients respond to ECT? The Nottingham results. *Journal of Affective Disorders* 33:245-250.

Prudic J, Sackeim H, Devanand D (1990). Medication resistance and clinical response to electroconvulsive therapy. *Psychiatry Research* 31:287-296.

Rich CL, Spiker DG, Jewell SW, Neil JF, Phillipson M (1986). ECT response in psychotic versus nonpsychotic unipolar depressives. *Journal of Clinical Psychiatry* 47:123-125.

Sackeim HA, Prudic J, Devanand DP, Decina P, Kerr B, Malitz S (1990). The impact of medication resistance and continuation pharmacotherapy on relapse following response to electroconvulsive therapy in major depression. *Journal of Clinical Psychopharmacology* 10:96-104.

Sackeim HA, Prudic J, Devanand DP, Nobler MS, Lisanby SH, Peyser S, Fitzsimons L, Moody BJ, Clark J. (2000). A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities [see comments]. *Archives of General Psychiatry* 57:425-434.

Schatzberg AF, Rothschild AJ. (1992). Psychotic (delusional) major depression: should it be included as a distinct syndrome in DSM-IV? *American Journal of Psychiatry* 149:733-745.

Sobin C, Prudic J, Devanand DP, Nobler MS, Sackeim HA (1996). Who responds to electroconvulsive therapy? A comparison of effective and ineffective forms of treatment. *British Journal of Psychiatry* 169:322-328.

Solan WJ, Khan A, Avery DH, Cohen S. (1988). Psychotic and nonpsychotic depression: comparison of response to ECT. *Journal of Clinical Psychiatry* 49:97-99.

8 | 1-Year follow-up after successful ECT: A naturalistic study in depressed inpatients

Journal of Clinical Psychiatry 2004; 65: 87-91

Tom K. Birkenhäger
Jan-Willem Renes
Esther M. Pluijms

Chapter 8.

1-Year follow-up after successful ECT: A naturalistic study in depressed inpatients

Tom K. Birkenhäger, Jan-Willem Renes, Esther M. Pluijms

Abstract

Background

The aim of this study is to examine both long-term efficacy of ECT and the predictive value of the adequacy of pre-ECT pharmacotherapy and the presence of delusions regarding post-ECT relapse in patients who suffered from major depressive disorder.

Method

Forty responders (a decrease in HRSD score ≥ 50%) to ECT were followed for one year, the majority prospective, and the remainder retrospective. Relapse is defined as either readmission or an obvious decline in social functioning or a change of antidepressant medication caused by a clear worsening of depressive symptoms.

Results

Both 6 and 12 months post-ECT relapse was significantly lower in patients with delusional depression compared with nondeluded patients: 3/24 (12%) versus 8/15 (53%) and 5/24 (21%) versus 11/15 (73%), respectively. Relapse rates for the whole sample are 11/39 (28%) at 6 months and 16/39 (40%) at 12 months. Regarding the impact of adequate pre-ECT antidepressant trials on relapse our data are inconclusive, because only a few patients did not receive adequate pharmacotherapy prior to ECT.

Conclusion

The remarkable finding of the present study is the favourable one-year outcome for patients with delusional depression. The relapse rate for patients adequately pretreated with antidepressants (45% over 1 year) is somewhat more favourable than expected.

Key words

Major depression; delusional depression; electroconvulsive therapy; pre-ECT pharmacotherapy; relapse

Introduction

Electroconvulsive therapy (ECT) is highly effective in severe depression, but since ECT is typically discontinued after successful treatment, relapse is a major problem.

Follow-up studies show that relapse-rates in the first 6 to 12 months after successful ECT are high, probably above 50% (Sackeim et al., 2001; Sackeim et al., 1990; Spiker et al., 1985). In most countries ECT is usually performed in depressed patients that were adequately pretreated with antidepressants. These are the patients who seem to be prone to relapse as Sackeim et al (Sackeim et al., 1990) demonstrated in a naturalistic follow-up study. Continuation treatment with tricyclic antidepressants may reduce post-ECT relapse, but certainly not to the level of 20% during the first 6 months, as early studies suggested (Bourgon and Kellner, 2000).

It is common practice to administer as continuation post-ECT pharmacotherapy the same class of antidepressant that was ineffective prior to ECT. The effectiveness of this strategy appears to be doubtful; Sackeim et al (Sackeim et al., 1990) found a 64% relapse rate in adequately pretreated patients during the first year post-ECT. In a randomised controlled double-blind study (Sackeim et al., 2001), nortriptyline-lithium combination was superior over both nortriptyline and placebo in preventing relapse, but 6 months post-ECT relapse rates were fairly high (39% versus 60%).

The results of the referred studies may not be applicable to the population of depressed patients in The Netherlands. In our country, little research has been done regarding the long-term efficacy of ECT, two studies (Verwey, 1991; Lemstra et al., 1996) finding a high relapse rate as well.

In The Netherlands ECT is an exceptional treatment administered almost exclusively to severely depressed inpatients in a limited number of hospitals, 300 patients receiving ECT nationwide in 1999 (*Annual Report of the National Commitee Evaluation of ECT*, 1999) on a population of 16.000.000 inhabitants.

Aim of the study

The present study is partially retrospective and evaluates the long-term efficacy of ECT in a setting, where patients receiving ECT are inpatients exclusively, the

majority showing a high degree of medication-resistance and many of them suffering from delusional depression.

Furthermore we wondered, whether the possible predictive value of illness characteristics regarding post-ECT relapse could be replicated in our patient sample.

We examined the impact of adequate pharmacotherapy prior to ECT (Sackeim et al., 1990) and the presence of delusions (Aronson et al., 1987; O'Leary and Lee, 1996; Spiker et al., 1985) on post-ECT relapse.

Method

Patient selection

We reviewed the case records of 69 consecutive inpatients that were successively treated with ECT between December 1993 and December 2000 at the inpatient unit for patients with severe depression of Parnassia Psychomedical centre, The Hague, the Netherlands. Eight patients with schizoaffective or bipolar disorder were excluded as well as six patients that had received a prior course of ECT.

Thus, 55 patients met the DSM III-R criteria for major depression and received their first ECT course, fulfilling the inclusion criteria prior to ECT. Because some patients were admitted and treated before the introduction of DSM-IV, we had to use DSM-IIIR criteria for the whole sample. To participate in this follow-up study, patients had to be classified as responders to ECT. Response to ECT was defined a priori as a reduction in the 17-item Hamilton Rating Scale for Depression (HRSD) score of at least 50% and a HRSD score of ≤ 14.

Forty of 55 patients responded to ECT (response rate: 40/55 = 73%) and entered the follow-up study. For a more detailed description of the acute treatment phase the reader is referred to a previous paper (Birkenhäger et al., 2003).

The adequacy of pre-ECT antidepressant trials was evaluated independently and rated by a psychiatrist (TKB) and a resident (EMP) using the Antidepressant Treatment History Form (ATHF) (Prudic et al., 1996; Sackeim et al., 1990). Patients scoring 3 or more on this 0-5 scale are classified as having received adequate treatment with antidepressants. A diagnosis of delusional depression was made only when the patient had expressed, either spontaneously or on inquiry definite mood-congruent delusions. Strong feelings of hopelessness and worthlessness were not considered sufficient for inclusion in the delusional sample. When the case records of an individual patient left any room for doubt about the presence of delusions, the patient was included in the non-deluded group. The relapse status was assessed by the second author (JWR).

Electroconvulsive therapy

Patients were withdrawn from all psychotropic medication at least one week before ECT and they were maintained drug-free during the course of ECT in all but five cases. These patients received 5 mg droperidol prior to ECT for severe anxiety. Two of them also received haloperidol 1-3 mg daily to control severe agitation. Eleven patients received right unilateral (RUL) (d'Elia) ECT only, another 11 patients initially received right unilateral ECT and were crossed over to bilateral ECT, because of insufficient response after three to 11 treatments and 18 patients received bilateral ECT from the start, because of the severity of the illness based on clinical observation.

ECT was administered with a brief-pulse, constant-current apparatus (Thymatron, Somatics, Lake Bluff, Il USA), with pulse width of 1.0 msec. The duration of the pulse train varied from 2.2 to 4.0 s. Patients received thiopental anaesthesia (1.0-2.5 mg/kg) and succinylcholine (1.0 mg/kg) for muscle relaxation. Physiological monitoring included pulse oximetry and an electrocardiogram (ECG). Seizure duration was determined by using a two-lead electroencephalography and the cuff technique. ECT was administered at a schedule of two treatments per week with moderate to high stimulus intensity (202-504 millicoulomb), without measuring seizure threshold by empirical dose titration. Stimulus dosing was based on age with a minimum of 252 millicoulomb in patients receiving RUL ECT. A motor seizure of less than 25 s was considered inadequate. The number of ECT treatments was determined by clinical observation and a minimum of 10 treatments was required before evaluation as a nonresponder. ECT was continued until patients were either asymptomatic or had not shown further improvement over three consecutive treatments.

Follow-up procedures

Following ECT patients stayed at the inpatient unit for approximately another 4-8 weeks, during which continuation pharmacotherapy was established. After their discharge from the inpatient unit the majority of the patients were treated either at the day care department or at the outpatient department of our hospital (n=28). Follow-up of these patients was prospective. The remaining 12 patients were treated at outpatient departments of referring psychiatric hospitals, their follow-up was retrospective. Because part of our sample was followed-up retrospectively we had to use rather obvious criteria for relapse. We defined relapse as either readmission, or the need for addition or change of antidepressant medication (not caused by side effects) or a clear decline in social functioning. Follow-up information was obtained

at least 12 months (range: 12-60 months) after the index ECT course. Prospective follow-up assessments were rated directly (n=28), retrospective follow-up assessments were obtained from collateral sources, namely the treating psychiatrist or general practitioner (n=12). Our hospital is one out of two providing ECT in the Southwest part of our country, therefore when a relapse was suspected, there was a strong tendency for patients to be referred back to our centre for evaluation.

Statistical analyses

Statistical analyses were performed using SPSS for windows, version 9.0.

For some patients it turned out to be difficult to assess the exact time of relapse, so we chose not to compute a survival analysis, but to evaluate relapse at 6 and 12 months post-ECT respectively. This could be done fairly accurately because literally all patients that relapsed did so in the first 8 months following ECT termination. Chi-square tests were used to analyze the difference in relapse rate between patients with delusional versus nondelusional depression as well as for medication-resistant versus nonmedication-resistant depressed patients. Fischer's exact tests (two-tailed) were used for two-by-two tables with cell frequencies lower than 5. Student's two-tailed t-tests were used to compare group means.

Results

The impact of delusions on relapse

The total patient sample for the follow-up study consisted of 40 inpatients, 27 women and thirteen men, with a mean age of 53.1 years (range 29-70 years). Twenty-five had suffered from delusional depression and 15 from depression without delusions. Table 1 shows the demographic and clinical characteristics for the total sample and as a function of either the presence or absence of delusions. The mean age was higher in the deluded group (56.0 versus 48.1 years; $p = 0.005$). Thirty-one patients were classified as having received adequate pre-ECT pharmacotherapy according to the ATHF, while the remaining 9 patients had received inadequate treatment with antidepressant medication prior to ECT. No difference was found concerning the proportion of adequately pretreated patients in the deluded and the non-deluded sample. Patients with delusions more frequently showed melancholic features: 24 of 25 patients (96%) versus 12 of 15 (80%) nondeluded patients, however this difference is not statistically significant (Fisher's exact test, $p = 0.14$). No significant difference in the number of patients achieving full remission (HRSD ≤ 7) at the end of the ECT course between both samples: 15 of 25 (60%) in the

deluded sample versus 7 of 15 (47%) in the sample without delusions (Fisher's exact test, p = 0.51).

Table 1 Demographic and clinical characteristics

Variable	Total sample (n=40)	Depressed with delusions (n=25)	Depressed without delusions (n=15)	P-value
Age in years, mean (S.D.)	53.1 (9.8)	56.0 (9.1)	48.1 (9.2)	0.005[a]
Female sex, n (%)	27 (67.5)	16 (64.0)	11 (73.3)	NS[b]
Adequate pre-ECT Pharmacotherapy, N (%)[c]	31 (77.5)	18 (72.0)	13 (86.6)	NS
Melancholic features, N (%)[d]	36 (90)	24 (96)	12 (80)	NS
Length of index Episode in months, Mean (S.D.)	21.7 (18.3)	16.1 (13.9)	31.0 (21.3)	0.011a
Pre-ECT HRSD score Mean (S.D.)	27.2 (5.4)	28.3 (5.9)	25.2 (3.8)	NS
Post-ECT HRSD score Mean (S.D.)	8.0 (3.3)	8.0 (2.9)	8.0 (3.6)	NS
Number of ECTs Mean (S.D.)	13.8 (4.3)	13.3 (4.5)	14.5 (4.1)	NS

[a]analyzed by Student's t-test [b]NS = not significant [c]patients were classified as meeting the ATHF criteria, when their rating was ≥3. [d]Meeting DSM-IIIR-criteria for melancholia

Patients without delusions had a significantly longer mean duration of their index depressive episode than the deluded patients (31.0 versus 16.1 months; p = 0.011).

The mean number of ECT treatments for patients with and without delusions was 13.3 and 14.5, respectively. Table 2 shows the relapse rates at 6 and 12 months for the total sample and as a function of either the presence or absence of delusions prior to ECT.

Table 2. Remission and relapse and the presence of delusions prior to ECT

	Total sample (n=39)	Depressed with delusions (n=24)	Depressed without delusions (n=15)	P-value
Remission at 6 months, N (%)	28 (72)	21 (88)	7 (47)	
Relapse at 6 months, N (%)	11 (28)	3 (12)	8 (53)	0.01[e]
Remission at 12 months, N (%)	23 (60)	19 (79)	4 (27)	
Relapse at 12 months, N (%)	16 (40)	5 (21)	11 (73)	0.002[e]

[e] Analyzed by Fischer's exact test

One female patient, who belonged to the group with delusions, was lost to follow-up. Eleven (28%) of the 39 remaining patients met criteria for relapse at the end of 6 months. Literally all patients relapsing did so in the first 8 months. Only three of the 24 (12%) patients with delusional depression relapsed within 6 months versus 8 of the 15 (53%) patients without delusions. Thus, the relapse rate is significantly lower in the deluded sample (Fischer's exact test, $p = 0.01$), even when the patient lost to follow-up would be considered as relapsed ($p= 0.03$). By the end of 12 months the general relapse amounted to 16 patients (40%), relapse rates for the groups with and without delusions were 5/24 (21%) and 11/15 (73%), respectively. Again, the relapse rate is significantly lower in patients with delusional depression (Fischer's exact test, $p= 0.002$).

The impact of pre-ECT pharmacotherapy on relapse

Table 3 shows the relapse rates at 6 and 12 months post-ECT for patients with and without pre-ECT adequate antidepressant trials according to the ATHF. The ratings of pre-ECT pharmacotherapy are dichotomised resulting in a relatively large

group of adequately pretreated patients, scoring ≥ 3 on the ATHF-scale and a small group without adequate prior pharmacotherapy. No relation between relapse rate at 6 and 12 months post-ECT and ATHF score was found, possibly because the group not meeting ATHF criteria was too small. It was impossible to analyse the relation between the score of the strongest medication trial as a continuous measure and post-ECT relapse, because the great majority of our sample had a score of 3 or 4. The relapse rate of patients with adequate pre-ECT pharmacotherapy amounted to 10/31 (32%) at 6 months and 14/31 (45%) at 12 months, which can be regarded as a rather favourable outcome for a medication resistant sample.

Table 3. Remission and relapse as a function of prior adequate antidepressant treatment[c]

	Total sample (n=39)	Pre-ECT adequate antidepressant trials (n=31)	Pre-ECT inadequate antidepressant trials (n=8)	P-value
Remission at 6 months, n (%)	28 (72)	21 (68)	7 (88)	
Relapse at 6 months, n (%)	11 (28)	10 (32)	1 (12)	0.40[e] = NS
Remission at 12 months, n (%)	23 (60)	17 (55)	6 (75)	
Relapse at 12 months, n (%)	16 (40)	14 (45)	2 (25)	0.43[e] = NS

[c]patients were classified adequately pretreated according to the ATHF when their rating on this scale was 3 or more [e]Analyzed by Fischer's exact test

Post-ECT pharmacotherapy

Three patients did not receive active medication, one patient refused continuation pharmacotherapy and two patients received placebo, while participating in a double-blind randomized study. Both patients taking placebo relapsed; one belonged to the sample with delusions, the other to the nondeluded sample. The patient without medication remained in remission. The majority of the patients on antidepressants were using imipramine or nortriptyline, at a dose sufficient to reach a therapeutic plasma level; only three patients were using an SSRI. Patients using lithium were kept on a therapeutic plasma level (0.6 - 1.0 mmol/l) as well. Continuation pharmacotherapy was based on the degree of medication resistance, possible partial

response to medication prior to ECT, type of pharmacotherapy which had not been tried before and patient preference. Thus it is impossible to draw any conclusions based on our data regarding the efficacy of the various types of continuation pharmacotherapy.

Discussion

In this study 60% of depressed inpatients, who responded to ECT remained well during the following year, while being on various types of continuation pharmacotherapy.

The relapse rate in our study sample is somewhat more favourable than those found in previous studies (Annual Report of the National Commitee Evaluation of ECT, 1999; Lemstra et al., 1996; Sackeim et al., 1990; Sackeim et al., 2000) particularly when the patients receiving adequate pre-ECT pharmacotherapy are considered. Our data show no relation between ATHF score and relapse rate.

There are several possible explanations for our results being more favourable than expected. Various aspects of the administration of ECT could influence post-ECT relapse. In the present study ECT was administered without concomitant benzodiazepines. In the study of Shapira et al (1995) no psychotropic drugs were allowed, but in the studies of Sackeim et al (1990; 2000) patients were allowed to use up to 3 mg of lorazepam daily, which may have reduced ECT response (Jha and Stein, 1996). With regard to post-ECT pharmacotherapy, all patients receiving antidepressant monotherapy or an antidepressant-lithium combination started using the antidepressant during the last two weeks of the ECT course, which may have prevented some of the early relapse. The remarkable finding from the present study is the significantly lower relapse rate in the sample with delusions compared to the nondeluded patients, both at 6 and 12 months post-ECT. This finding is contradictory to the results of some of the previous studies (Aronson et al., 1987; O'Leary and Lee, 1996; Spiker et al., 1985). However, these studies did not include a nondelusional control group. In other studies no difference in relapse (Sackeim et al., 1990) was found in delusional and nondelusional patients. Furthermore, in a recent study a lower relapse rate was found in psychotically depressed patients (Sackeim et al., 2001).

There are a several possible explanations for the differences in relapse rates among studies. Suboptimal administration of ECT could have influenced the results of earlier studies, for instance the administration of low dosage unilateral ECT could lead to an incomplete remission and consequently to relapse-proneness. Eleven

patients in this study were treated with RUL ECT only, without empirical dose titration, so the number of patients receiving more than 5x seizure threshold is unknown. Therefore, an unknown proportion of them may have received an inadequate ECT course. If bilateral ECT had been used in all patients, the number of patients achieving full remission might have been higher and consequently the number of patients relapsing might have been reduced. Furthermore the mean number of ECTs probably had been considerably lower, as shown by a recent study (Petrides et al., 2001). In the present study we included only delusional depressed patients with mood-congruent delusions. In none of the studies reviewed the qualification mood-congruence with regard to delusions is mentioned. Depressed patients with delusions that are not mood-congruent may show a less complete response to ECT and therefore be more prone to relapse. A relevant confounding factor in the present study that may have influenced the relapse rate to the disadvantage of the nondeluded sample is the finding that this sample had a significantly longer mean duration of the index depressive episode. An alternative explanation for the favourable outcome in patients with delusional depression would be an underreporting of relapse in patients whose follow-up was retrospective. This explanation is considered rather unlikely, as far as the delusional sample is concerned, because if patients who suffered from psychotic depression experience a relapse or recurrence it nearly always has psychotic features (Schatzberg and Rothschild, 1992).

Although in the present study the relapse rate post-ECT is more favourable than those found in previous studies (Annual Report of the National Commitee Evaluation of ECT, 1999; Sackeim et al., 2001; Sackeim et al., 1990; Sackeim et al., 2000) relapse after successful ECT remains a major problem. Several strategies that could possibly reduce post-ECT relapse warrant further study. Such as starting an antidepressant during the final 2 weeks of ECT, which was done in the present study and adding lithium to the antidepressant as soon as ECT is terminated. The application of continuation ECT may also reduce relapse after successful ECT. This treatment was not used in the present study, because in the Netherlands continuation ECT is just originating, it is offered only to patients who relapsed after successful ECT while on post-ECT pharmacotherapy. Finally Sackeim et al (Sackeim et al., 2001) proposed an interesting strategy: they suggested tapering ECT over a few weeks instead of the standard abrupt discontinuation of an ECT course. Since our study is descriptive rather than predictive, our findings regarding the more favourable one-year outcome in delusional depression need to be confirmed by larger fully prospective studies.

References

Annual Report of the National Commitee Evaluation of ECT. (1999). The Hague: National Committee Evaluation ECT.

Aronson TA, Shukla S, Hoff A (1987). Continuation Therapy After ECT for Delusional Depression: A Naturalistic Study of Prophylactic Treatments and Relapse. *Convulsive Therapy* 3:251-259.

Birkenhäger TK, Pluijms EM, Lucius SA. (2003). ECT response in delusional versus non-delusional depressed inpatients. *Journal of Affective Disorders* 74:191-195.

Bourgon LN, Kellner CH. (2000). Relapse of depression after ECT: a review. *Journal of Electroconvulsive Therapy* 16:19-31.

Jha A, Stein G (1996). Decreased efficacy of combined benzodiazepines and unilateral ECT in treatment of depression. *Acta Psychiatrica Scandinavica* 94:101-104.

Lemstra A, Leentjens AF, Van den Broek WW. (1996). Temporary results only in electroconvulsive therapy in therapy-resistant depression; retrospective study. *Nederlands Tijdschrift voor Geneeskunde* 140:260-264.

O'Leary DA, Lee AS (1996). Seven year prognosis in depression. Mortality and readmission risk in the Nottingham ECT cohort. *British Journal of Psychiatry* 169:423-429.

Petrides G, Fink M, Husain MM, Knapp RG, Rush AJ, Mueller M, Rummans TA, O'Connor KM, Rasmussen KG Jr, Bernstein HJ, Biggs M, Bailine SH, Kellner CH (2001). ECT remission rates in psychotic versus nonpsychotic depressed patients: a report from CORE. *Journal of Electroconvulsive Therapy* 17:244-253.

Prudic J, Haskett RF, Mulsant B, Malone KM, Pettinati HM, Stephens S, Greenberg R, Rifas SL, Sackeim HA (1996). Resistance to antidepressant medications and short-term clinical response to ECT. *American Journal of Psychiatry* 153:985-992.

Sackeim HA, Haskett RF, Mulsant BH, Thase ME, Mann JJ, Pettinati HM, Greenberg RM, Crowe RR, Cooper TB, Prudic J (2001). Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. *Journal of the American Medical Association* 285:1299-1307.

Sackeim HA, Prudic J, Devanand DP, Decina P, Kerr B, Malitz S. (1990). The impact of medication resistance and continuation pharmacotherapy on relapse following response to electroconvulsive therapy in major depression. *Journal of Clinical Psychopharmacology* 10:96-104.

Sackeim HA, Prudic J, Devanand DP, Nobler MS, Lisanby SH, Peyser S, Fitzsimons L, Moody BJ, Clark J (2000). A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities [see comments]. *Archives of General Psychiatry* 57:425-434.

Schatzberg AF, Rothschild AJ (1992). Psychotic (delusional) major depression: should it be included as a distinct syndrome in DSM-IV? *American Journal of Psychiatry* 149:733-745.

Shapira B, Gorfine M, Lerer B (1995). A prospective study of lithium continuation therapy in depressed patients who have responded to electroconvulsive therapy. *Convulsive Therapy* 11:80-85.

Spiker DG, Stein J, Rich CL (1985). Delusional Depression and Electroconvulsive Therapy: One Year Later. *Convulsive Therapy* 1:167-172.

Verwey B (1991). Electroconvulsive therapy in non-university hospitals. *Nederlands Tijdschrift voor Geneeskunde* 135:1694-1697.

9 | Continuation pharmacotherapy after successful ECT, a randomized placebo controlled trial

Submitted for publication

Walter W. van den Broek
Tom K. Birkenhäger
Paul G.H. Mulder
Jan A. Bruijn
Peter Moleman

Chapter 9

Continuation pharmacotherapy after successful ECT, a randomized placebo controlled trial

Walter W. van den Broek, Tom K. Birkenhäger, Paul G.H. Mulder, Jan A. Bruijn, Peter Moleman

Abstract

Background

To compare imipramine with placebo in preventing relapse after successful ECT in medication resistant depressive inpatients.

Methods

Double blind placebo controlled study of 6 months after successful ECT. Medication resistance was assessed with the Antidepressant Treatment History Form (ATHF). The outcome criterion was a score of at least moderately worse compared to baseline on the Clinical Global Impression Scale (CGIS). Treatments were compared with survival analysis using the Cox Proportional Hazards Model including as prespecified co variables: psychotic features and the score on the Hamilton Rating Scale for Depression (HRSD) at the start of the trial.

Results

Relapse occurred in 2 of 11 patients on imipramine and 12 of 15 patients on placebo, a significant difference. The change of relapse was positively correlated with a higher HRSD at the start of the trial. Psychotic features did not significantly affect the change of relapse.

Conclusions

In medication resistant depressed inpatients continuation therapy with a tricyclic antidepressant with adequate plasma levels after successful ECT can prevent relapse. This favorable result could be explained by our study population which included patients never being treated with ECT before and by optimal ECT treatment. We used an optimal dosage strategy with unilateral ECT, 74 % were treated with bilateral ECT and the use of benzodiazepines was prohibited.

Treatment of these patients with ECT should be rigorous since optimal outcome with ECT is related to a lesser change of relapse.

Keywords

Electroconvulsive therapy, depressive disorder, follow-up, pharmacotherapy, placebo.

Introduction

The indication for Electroconvulsive therapy (ECT) is usually medication-resistant depressive disorder (American Psychiatric Association, 2001). Although many patients receive ECT after antidepressants have failed, medication is often reinstalled to prevent relapse after successful ECT. However the evidence supporting this practice is based on studies performed at a time ECT was used as the treatment of first choice, not only for treatment resistant patients (Imlah et al., 1965; Kay et al., 1970; Seager and Bird, 1962). Medication was started at the same time as ECT. Patients may have benefited from the antidepressant medication as much as from ECT, which precludes conclusions with regard to prevention of relapse in patients responding to ECT and not responding to antidepressants. A recent report suggests poor relapse prevention from antidepressant medication after ECT in patients with antidepressant resistant depression (Sackeim et al., 1990).

In recent years ECT has been used in the Netherlands for patients not responding to consecutive trials of selective serotonin re-uptake inhibitors, tricyclic antidepressants, tricyclic antidepressants in combination with lithium addition and monoamine oxidase inhibitors. In view of this rigorous pretreatment we hypothesized that imipramine would not differ from placebo in preventing relapse after succesful ECT. Since psychotic depressive episodes respond particulary favorabel to ECT (Avery and Lubrano, 1979; Buchan et al., 1992), psychotic features were included in the analysis as a co variable.

We choose imipramine as the antidepressant since tricyclic antidepressants (TCAs) were used in earlier trials (Imlah et al., 1965; Kay et al., 1970; Seager and Bird, 1962) and modern antidepressants may be less effective than TCAs in treatment of severe depressed inpatients (Anderson, 2000; Bruijn et al., 1999; DUAG, 1986, 1990; Roose et al., 1994).

Methods

The study was performed in two centers, at the department of Psychiatry of the Erasmus Medical Centre in Rotterdam (ErasmusMC) and at Parnassia Psychomedical Centre (PPC) in The Hague. Both units have a regional function for

treatment of uncomplicated depressed patients and a super-regional function for treatment of therapy-resistant depressed patients. Patients were enrolled in the study from April 1997 to July 2001.

Included were patients aged 18-65 years who had a DSM IV diagnosis of "depressive episode" (APA, 1994) and at least a treatment with a TCA or fluvoxamine with adequate plasma levels during four weeks during the current episode. The diagnosis was assessed after a drug free period of at least 5 days with the depression part of the Schedule for Affective Disorders and Schizophrenia (Spitzer and Endicot, 1978). Three research psychiatrists (WvdB, JB in ErasmusMC and TB in PCC) did all assessments. Excluded were patients with schizophrenia, bipolar or schizo-affective disorder, organic brain syndrome, chronic alcohol or drug abuse, and presence of absolute contraindication for imipramine, pregnancy or the risk to become pregnant or if treated with ECT during the current episode. To enter the relapse prevention trial, patients had to respond to ECT with at least a 50% reduction in the score on the 17 item Hamilton Rating Scale for Depression (HRSD) relative to pre-ECT baseline, with a maximum score of 16 both within two days after ECT and in a reassessment of one week after discontinuation of ECT while free of psychotropic medication. Remission was defined as a HRSD score of seven or less after the last ECT treatment and in a reassessment of one week after discontinuation of ECT while free of psychotropic medication.

The Ethics Committee of the Erasmus Medical Centre Rotterdam approved the protocol. The protocol was carried out in accordance with the ethical standards laid down in the declaration of Helsinki. Patients provided informed consent both before ECT and the relapse prevention phase.

Prior to ECT medication resistance during the index depressive episode was evaluated. The strongest antidepressant medication trial was scored using the Antidepressant Treatment History Form (ATHF) (Keller et al., 1986; Prudic et al., 1996; Sackeim et al., 1990). Patients with at least one antidepressant trial of any type with a rating of 3 or higher were classified as medication resistant. The remainder were classified as having received inadequate antidepressant pharmacotherapy before ECT (Prudic et al., 1996; Prudic et al., 1990). In table 1 medication trials before ECT during the index episode are presented for all patients included in this trial.

ECT was administered with a brief pulse, constant current apparatus (Thymatron DGx, Somatics Inc., 910 Sherwood Drive, Lake Bluff, IL 60044). Seizure threshold was determined during the first session with stimulus titration.

Table 1. Pretreatment before ECT, ATHF score, treatment after ECTand relapse.

Patient	Fluvoxa-Mine	TCA	Lithium addition	MAO inhibitor (dosage)	ATHF	Random	Relapse
1		+	+	+ (90 mg)	4	Placebo	+
2	+		+	+ (100 mg)	4	Imipramine	Drop out
3		+	+	-	4	Imipramine	-
4	+		+	+ (100 mg)	4	Placebo	+
5	+		+	+ (100 mg)	4	imipramine	-
6		+	+	+ (80 mg)	5	Imipramine	-
7	+		+	+ (60 mg)	5	Placebo	+
8		+	+	+ (80 mg)	5	Imipramine	+
9		+	+	+ (60 mg)	5	Placebo	+
10	+		+	-	4	Imipramine	-
11		+	+	-	2	Placebo	-
12		+	+	+ (60 mg)	5	Placebo	+
13		+	-	+ (100 mg)	4	placebo	+
14		+	+	+ (80 mg)	1	Imipramine	-
15		+	+	+ (100 mg)	2	Placebo	-
16		+	-	+ (100 mg)	4	Imipramine	-
17		+	-	+ (80 mg)	3	Imipramine	-
18		+	+	+ (100 mg)	4	Placebo	-
19		+	+	+ (70 mg)	4	Placebo	+
20		+	+	+ (100 mg)	4	Imipramine	+
21		+	+	+ (80 mg)	1	Imipramine	-
22		+	+	+ (80 mg)	5	Placebo	+
23		+	+	+ (60 mg)	2	Placebo	+
24		+	+	+ (90 mg)	2	Placebo	+
25		+	+	+ (80 mg)	1	Imipramine	-
26		+	+	+ (100 mg)	1	Placebo	+
27		+	+	+ (100 mg)	4	placebo	+

ATHF= Antidepressant Treatment History Form
Fluvoxamine with at least 4 weeks of adequate plasma level
TCA=Tricyclic Antidepressant with at least four weeks of adequate plasma levels
Lithium addition is with at least three weeks lithium plasma level > 0.7 mmol/l
MAO inhibitor = Monoamine Oxydase inhibitor at least during four weeks with the mentioned dosage.

If the starting stimulus dose failed to elicit a seizure of at least 25 seconds duration measured with the cuff method, stimulus charge was increased according to the titration schedule and the patient was re-stimulated after 30 seconds. Seizure

threshold was defined as the stimulus dosage that elicited a seizure of at least 25 seconds according to the cuff method. For right unilateral treatment, dosage at subsequent treatment exceeded initial threshold by at least 250%, for bilateral treatment 150%. During the course of ECT, stimulus dosage settings were adjusted upward in order to maintain seizure duration of at least 25 seconds as measured with the cuff method. Patients were initially treated with right unilateral ECT; patients were crossed over to bilateral ECT if response was inadequate after six treatments. Patients in a critical condition started with bilateral ECT.

Anesthesia was achieved during the ECT sessions with intravenous (i.v.) administration of metoclopramide 10 mg, glycopyrrolate 0.002-0.003 mg/kg, a bolus injection of alfentanil 0.010-0.015 mg/kg and etomidate 0.2-0.3 mg/kg followed by succinylcholine 0.5-1.0 mg/kg. Patients were treated twice weekly, clinical evaluation of treatment was performed each week using the HRSD and Clinical Global Impression scale (CGIS) (Guy, 1976).

Patients were withdrawn from medication before ECT and were maintained medication free during the course of ECT; in case of severe agitation incidental use of haloperidol was allowed.

After response or remission with ECT patients who gave informed consent were randomized either to placebo or imipramine.

Tablets identical in appearance, weight and taste containing either imipramine or placebo were administered once a day at 10 p.m., starting with 75 mg. The pharmacist did the preparation of the tablets and the randomization from a random number table. After two days, the dose was doubled unless severe side effects were observed. Blood levels were monitored once a week by the pharmaceutical laboratory of the ErasmusMC until discharge from hospital with a steady dosage and blood level. The hospital pharmacist advised on the adjustment of the dosage, based on the targeted blood level according to a predefined dosage table for imipramine and a variable dosing table for the placebo. This was communicated to the treating physician in percentages in order to prevent unblinding. The treating physicians were not involved in the ratings of this study.

The predefined blood level for imipramine + desimipramine was 200-300 ng/ml (100% equals 250 ng/ml).

Patients were evaluated every four weeks for 6 months after inclusion by WvbB and TKB who were blind to the treatment condition. At each visit, the HRSD and CGIS were completed. Relapse was defined as at least "moderately worse" according to the CGIS. During the trial, interrater sessions with the investigating psychiatrists took place 6 times a year. The sum of all HDRS items of the three research

psychiatrists was used to test interrater reliability (kappa=0.95).

Assuming a relapse rate of 50% with placebo and 20% with imipramine the goal was to enroll at least 37 patients in each randomized condition to have at least an 80% probability of detecting a significant difference.

The efficacy of both treatments was compared with survival analysis using the Cox Proportional Hazards Model with duration of treatment until relapse as the survival time variable. An event was scored the first time a patient met the relapse criterion. Dropouts without relapse were censored at the time of dropout. Patients without relapse were censored at the end of the trial. The following prespecified co variables were included along with treatment: psychotic features and HRSD score at the start of the trial. Statistical significance was defined as $p<0.05$ (two-sided). The data were analyzed using SPSS version 10 for Windows.

Results

After a drug free period 114 patients were diagnosed with depressive disorder first episode or unipolar disorder. From the eligible 47 patients, 27 were randomized (Figure 1).

The characteristics of these patients are summarized in table 2. There were no significant differences between treatment groups. None of the responders relapsed in the first week after discontinuation of ECT. Seven (26%) patients were treated solely with unilateral electrode placement all others were started (13, 48%) or switched (7, 26%) to bilateral ECT. The mean number of treatments was 12.51. None of the patients received ECT in a prior episode. One patient could not discontinue the benzodiazepine; two patients received haloperidol during ECT.

Table 2. Patient characteristics for continuation treatment groups

Random	Placebo (n=15)	Imipramine (n=12)
Age, mean (range) in years	51.5 (36-64)	51.3 (36-60)
Women, %	10 (71%)	10 (83%)
Psychotic	4 (27%)	5 (42%)
Pre-ECT Hamilton Rating Scale for Depression, mean ± SD	28.6 ± 6.4	27.1 ± 6.5
Post ECT Hamilton Rating Scale for Depression, mean ± SD	5.9 ± 3.8	4.9 ± 2.5
Episode duration < 1 year	4	5

ECT= electroconvulsive therapy
SD= Standard Deviation

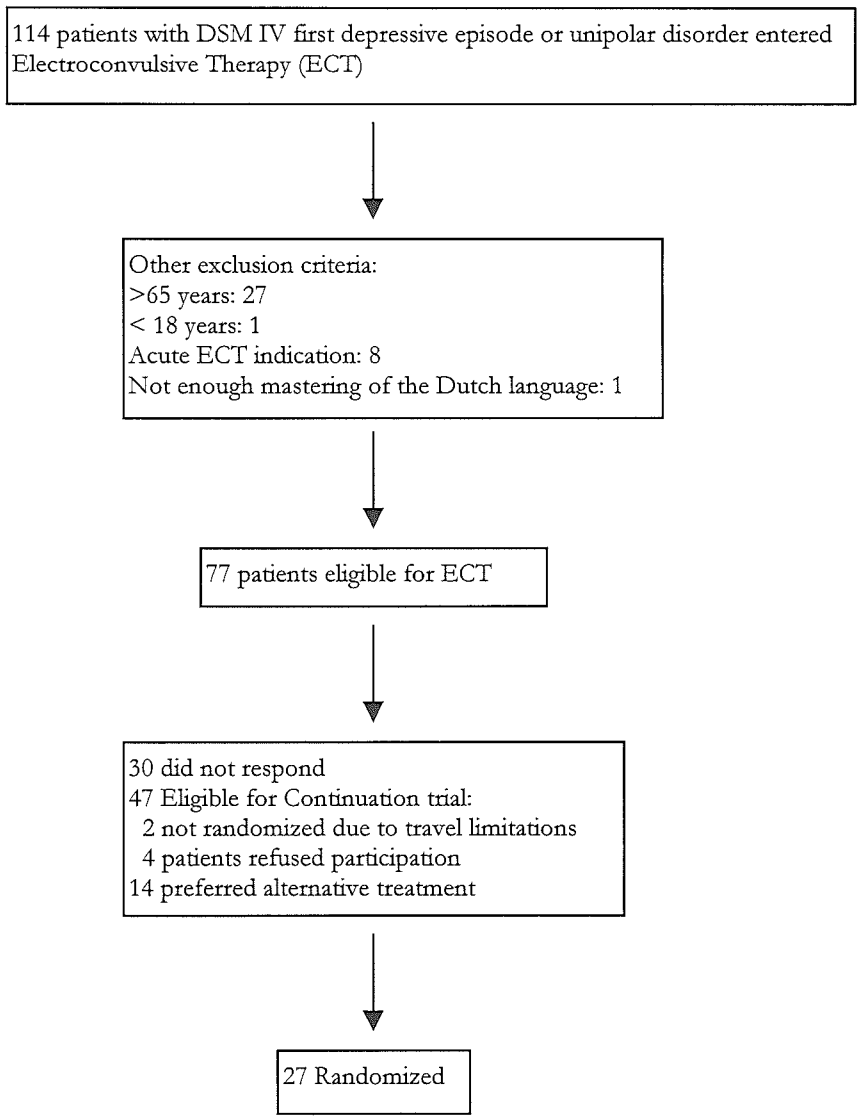


Figure 1. Participant flow

One patient refused further participation just after randomization. The Cox regression analysis using relapse defined as at least "moderately worse" according to the CGIS, with the type of treatment as independent variable shows a significant difference in favor of imipramine. In the placebo group 12 out of 15 patients relapsed as compared to 2 out of 11 in the imipramine group. With regard to the prespecified co variables, the analysis showed a significant effect on relapse of HRSD before the start of the trial but not for psychotic features. Imipramine treatment lowers the risk of relapse with 85.6 % compared to placebo (95% Confidence Interval: 24.6%-97.2%) adjusted for the co variables mentioned.

Discussion

In contrast to expectations, imipramine effectively prevented relapse after successful ECT in contrast to placebo. This is surprising since most patients were treated unsuccessfully with imipramine or a similar tricyclic antidepressant with adequate plasma levels during four weeks and even lithium addition with adequate plasma levels during three weeks as inpatients (19/27) (table 2) before they were treated successfully with ECT. The high relapse rate in the placebo group emphasizes the need of continuation therapy after ECT for patients with antidepressant resistant depressive episodes. Previous research suggested that continuation therapy with a TCA reduced relapse rate to 20% comparable to the result of our trial with imipramine (18%) (Imlah et al., 1965; Kay et al., 1970; Seager and Bird, 1962). In contrast to this earlier research, we adjusted the dosage of imipramine to predefined adequate plasma levels. This could explain the favorable result comparable to earlier trials were ECT was used as the first line of treatment mostly in combination with TCAs.

Recently two other placebo controlled trials after successful ECT were published (Lauritzen et al., 1996; Sackeim et al., 2001). Relapse prevention with nortriptyline (60% relapse) was significantly more efficacious compared to placebo (84% relapse), the combination of nortriptyline and lithium being even more effective (39% relapse) (Sackeim et al., 2001). Although nortriptyline dosage was also adjusted to plasma levels the relapse rate was higher compared to our imipramine group. Different outcome measures were used in this trial (Sackeim et al., 2001). Relapse was defined as a mean score of at least 16 on the HRSD 24 item version that was at least maintained over 2 consecutive visits (1 week) and a mean absolute increase of 10 points at 2 consecutive visits relative to continuation trial baseline. The difference in outcome with our trial could be explained by difference in study population. Our

patients were ECT naïve; none of the patients were treated with ECT before during an earlier episode compared to 40-50% of patients in this recent study (Sackeim et al., 2001). Our patients were rigorously pretreated with antidepressants, but were never treated with ECT before. One could argue that pretreatment with ECT during an earlier episode makes relapse prevention after ECT during later episodes more difficult. This subject should be explored more thoroughly with further research.

One other explanation could be a more optimal treatment with ECT. We used a more efficacious dosage strategy with unilateral electrode placement; eventually 74 % were treated with bilateral ECT and higher mean ECT sessions. Bilateral electrode placement with ECT is considered very effective (Sackeim et al., 1993; Sackeim et al., 2000). Benzodiazepines were not allowed during our ECT treatment instead of allowing lorazepam (up to 3 mg/day) as needed. The use of benzodiazepines during ECT has a negative influence on outcome (Jha and Stein, 1996).

The change of relapse was significantly higher with higher HRSD scores at the start of the continuation trial, this result is in agreement with the previous mentioned trial (Sackeim et al., 2001).

The other trial compared paroxetine with placebo after successful ECT. Medication was started before ECT; patients were allocated to the placebo versus paroxetine group if there was a contraindication for the use of imipramine. Patients knew to which group they were assigned (placebo versus paroxetine or paroxetine versus imipramine). Statistical significance was defined as p-value<0.05 with one tailed tests in the placebo controlled group. ECT procedures used for stimulus dosage and electrode placement are considered less effective as normally used in ECT trials (Lauritzen et al., 1996). The survival curves for paroxetine and placebo differed significantly only after three months, this significant difference disappeared after 6 months. Due to the here for mentioned shortcomings of this trial a comparison with our results cannot be made.

Imipramine effectively prevented relapse after successful ECT with medication resistant depressed inpatients as compared to placebo. This result is in contrast with a comparable study. This could be explained by our study population which included patients never being treated with ECT before and by optimal ECT treatment. We used a more optimal dosage strategy with unilateral ECT, 74 % were treated with bilateral ECT and benzodiazepines as needed were prohibited. This trial also shows that optimal result with ECT should be achieved in order to prevent relapse as much as possible. Rigorous treatment with ECT is of major importance with medication resistant patients.

References

Anderson IM (2000). Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. *Journal of Affective Disorders* 58:19-36.

American Psychiatric Association (1994). *Diagnostic and statistical manual of mental disorders* (4th ed). Washington DC: American Psychiatric Association.

American Psychiatric Association (2001). *The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training and Privileging* (2nd ed). Washington, DC: American Psychiatric Association Committee on Electroconvulsive Therapy.

Avery D, Lubrano A (1979). Depression treated with imipramine and ECT: the DeCarolis study reconsidered. *American Journal of Psychiatry*, 136:559-562.

Bruijn JA, Moleman P, Mulder PG, Van den Broek WW (1999). Depressed in-patients respond differently to imipramine and mirtazapine. *Pharmacopsychiatry* 32:87-92.

Buchan H, Johnstone E, McPherson K, Palmer RL, Crow TJ, Brandon S (1992). Who benefits from electroconvulsive therapy? Combined results of the Leicester and Northwick Park trials. *British Journal of Psychiatry* 160:355-359.

DUAG (1986). Citalopram: clinical effect profile in comparison with clomipramine. A controlled multicenter study. Danish University Antidepressant Group. *Psychopharmacology* 90:131-138.

DUAG (1990). Paroxetine: a selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. Danish University Antidepressant Group. *Journal of Affective Disorders* 18:289-299.

Guy W (1976). *Assessment manual for psychopharmacology*. Rochville: U.S. Department of Healthy Education and Welfare.

Imlah N, Ryan E, Harrington J (1965). The influence of antidepressant drugs on the response to electroconvulsive therapy and on subsequent relapse rates. *Neuropsychopharmacology* 4: 438-442.

Jha A, Stein G (1996). Decreased efficacy of combined benzodiazepines and unilateral ECT in treatment of depression. *Acta Psychiatrica Scandinavica* 94:101-104.

Kay D, Fahy T, Garside R (1970). A seven-month double-blind trial of amitriptyline and diazepam in ECT-treated depressed patients. *British Journal of Psychiatry* 117:667-671.

Keller MB, Lavori PW, Klerman GL, Andreasen NC, Endicott J, Coryell W, Fawcett J, Rice JP, Hirschfeld RM (1986). Low levels and lack of predictors of somatotherapy and psychotherapy received by depressed patients. *Archives of General Psychiatry* 43:458-466.

Lauritzen L, Odgaard K, Clemmesen L, Lunde M, Ohrstrom J, Black C, Bech P (1996). Relapse prevention by means of paroxetine in ECT-treated patients with major depression: a comparison with imipramine and placebo in medium-term continuation therapy. *Acta Psychiatrica Scandinavica* 94:241-251.

Prudic J, Haskett RF, Mulsant B, Malone KM, Pettinati HM, Stephens S, Greenberg R, Rifas SL, Sackeim HA (1996). Resistance to antidepressant medications and short-term clinical response to ECT. *American Journal of Psychiatry* 153:985-992.

Prudic J, Sackeim H, Devanand D (1990). Medication resistance and clinical response to electroconvulsive therapy. *Psychiatry Research* 31:287-296.

Roose SP, Glassman AH, Attia E, Woodring S (1994). Comparative efficacy of selective serotonin reuptake inhibitors and tricyclics in the treatment of melancholia. *American Journal of Psychiatry* 151:1735-1739.

Sackeim HA, Haskett RF, Mulsant BH, Thase ME, Mann JJ, Pettinati HM, Greenberg RM, Crowe RR, Cooper TB, Prudic J (2001). Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. *Journal of the American Medical Association* 285:1299-1307.

Sackeim HA, Prudic J, Devanand DP, Decina P, Kerr B, Malitz S (1990). The impact of medication resistance and continuation pharmacotherapy on relapse following response to electroconvulsive therapy in major depression. *Journal of Clinical Psychopharmacology* 10:96-104.

Sackeim HA, Prudic J, Devanand DP, Kiersky JE, Fitzsimons L, Moody BJ, McElhiney MC, Coleman EA, Settembrino JM (1993). Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy [see comments]. *New England Journal of Medicine* 328:839-846.

Sackeim HA, Prudic J, Devanand DP, Nobler MS, Lisanby SH, Peyser S, Fitzsimons L, Moody BJ, Clark J (2000). A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities [see comments]. *Archives of General Psychiatry* 57:425-434.

Seager C, Bird R (1962). Imipramine with electrical treatment in depression: a controlled trial. *Journal of Mental Sciences* 108:704-707.

Spitzer R, Endicot J (1978). *Schedule for Affective Disorders and Schizofrenia (SADS)* (3rd ed). New York: Biometric Research, New York State Psychiatric Institute.

10 Summary and general discussion

Chapter 10.

Summary and general discussion

During the last decades several new agents have been introduced for the treatment of depressive disorders. Compared with the classical tricyclic antidepressants (TCAs), these newer agents have different side-effects and very low toxicity. Although these new antidepressants are slightly better tolerated than TCAs, their appearance has not resulted in higher efficacy. Generally, 30-40 % of patients will fail to respond to an adequate trial of an antidepressant, and an additional problem is partial response (Keller et al., 1984; Paykel et al., 1995).

Treatment of depressed inpatients is a challenge because these patients are severely depressed with typical inpatient characteristics, including suicidality, melancholic and/or psychotic features, long illness duration and adequate previous treatment with a new antidepressant during the current episode.

Optimal treatment of these patients is the topic of this thesis. Important concepts in the treatment of these depressed patients are adequate treatment and an effective treatment strategy.

The concept of adequate treatment has a number of parameters. Firstly, the treatment should be appropriate to the diagnosis. Patients admitted to the participating centers are made medication-free and subjected to a drug-free observation period to confirm the diagnosis of depression. The treatment is given in an adequate amount and for a sufficient duration.

The treatment strategy for depressed inpatients in the Netherlands is based on the CBO (Kwaliteitsinstituut voor de gezondheidszorg) consensus of 1995 (De Groot, 1995). This strategy consists of the following four steps: a TCA as the drug of first choice, followed by lithium addition to that drug if response had been absent or partial. In case of a lack of response to the two-step strategy, this is followed by treatment with an irreversible monoamine oxidase (MAO) inhibitor succeeded by electroconvulsive therapy (ECT) if response to the latter was insufficient.

The work presented here focuses on each of these steps in the treatment of depressed inpatients. The first important topic is to establish the difference in efficacy and tolerability between a TCA and a serotonin reuptake inhibitor (SSRI), with dose adjustment of both drugs to a predefined blood level.

Lithium is known to augment the therapeutic effect of several antidepressants, including several SSRIs (Baumann et al., 1996; Katona, 1995). however, up to now it is still unclear whether there is a difference between the two treatment strategies, imipramine followed by lithium addition, or fluvoxamine (an SSRI) followed by lithium addition. The effect of MAO inhibitors is the least studied step in our algorithm. ECT is usually the last step in case of treatment-resistant depression and its effect is probably negatively influenced by the pretreatment before ECT, i.e. the more pretreatment the least efficacy and more relapse during follow-up. This topic and the safety of ECT were the last questions to be addressed in this thesis.

This chapter summarizes and discusses the main findings of the studies presented in this thesis. The clinical implications of our findings are addressed and recommendations are made for future research.

Chapter 2 presents a study showing a significant difference between imipramine and fluvoxamine in change of illness severity in favor of imipramine. The other *a priori* defined outcome criterion, a reduction of > 50% on the Hamilton Rating Scale of Depression (HRSD) showed no significant difference. The mean reduction on the HRSD was significantly larger in the imipramine group than in the fluvoxamine group.

An earlier investigation with a study design similar to ours showed that a new antidepressant (mirtazapine) was less effective compared to imipramine (Bruijn et al., 1996). A recent meta-analysis has shown that the efficacy of TCAs is superior over that of SSRIs in depressed inpatients (Anderson, 2000). In contrast to the studies included in the meta-analysis, in our trial the SSRI fluvoxamine was dosed with targeted blood levels.

For several reasons dose adjustment to targeted TCA blood levels is necessary in depressed inpatients. In studies with a flexible-dose design most patients on TCAs will finish their treatment on doses that are too low to test the efficacy of these drugs. A fixed dose of 200 mg a day will result in a therapeutic blood level of imipramine in only 60% of the patients (Glassman et al., 1977). Treatment with a flexible dose will result in only 30% of the patients having a therapeutic blood level (Moleman et al., 1996). Besides the risk of underdosing the TCA, dosing with targeted blood levels ensures compliance, drug interaction monitoring and usually leads to faster adjustment to an adequate dosage. Imipramine shows sigmoid relationship between blood level and clinical outcome. When the level of imipramine and its demethylated metabolite exceeds 200 ng/ml, the number of patients responding is significantly higher compared to patients with plasma levels below that

level. Raising the plasma level above 250 ng/ml, although producing more side-effects, did not increase the number of patients responding favorably (Glassman et al., 1977; Reisby et al., 1977).

There is also some evidence for a plasma level effect relationship with fluvoxamine (Foglia et al., 1990; Walczak et al., 1996). However, routine drug monitoring of fluvoxamine is not common practice. Therapeutic drug monitoring of fluvoxamine may be useful in situations where non-compliance is suspected, liver failure exists, in the presence of toxic events, and with therapeutic failure (DeVane and Gill, 1997; Rasmussen and Brosen, 2000). In our opinion, efficacy trials with fluvoxamine may be added to these latter indications because treatment for such a severe and dangerous disease with inpatients counterbalances the costs and risks these patients are subjected to.

The finding of a significant difference between imipramine and fluvoxamine in this trial, even with optimal dosing and ruling out non-compliance, was possible due to the optimal design of the trial. Contributing methodological factors were the use of minimal concurrent psychopharmacological medication and a low drop-out rate.

Each or all of the above-mentioned factors may be instrumental in the discriminative power of the trial.

In *chapter 3* the efficacy of imipramine and subsequent lithium addition in non-remitters was shown to be superior over a similar strategy with fluvoxamine.

The present study is the first to compare a TCA with an SSRI, both followed by lithium addition. Lithium addition is a preferred strategy for antidepressant-refractory depression. It has considerable advantages compared with a change of antidepressants: e.g. time is saved because there is no need for tapering the previous treatment or for a wash-out period. Moreover, possible partial response to the antidepressant is preserved.

Previous studies on lithium addition included non-responders to antidepressants for which response rate and drop-out percentage of the preceding antidepressant treatment were not reported (Bauer and Dopfmer, 1999). The efficacy of lithium addition can be evaluated properly only if the preceding treatment with the antidepressant is optimal. This was achieved in the first phase of the present study. When considering lithium addition separately, the remission rate to imipramine-lithium (71%) was again superior to that of fluvoxamine-lithium (47%).

The literature is somewhat divided regarding the speed of onset of the effect of lithium addition. An early study (De Montigny et al., 1981) reported a high frequency of response within 48 hours, whereas later placebo-controlled studies (Katona et al., 1995; Stein and Bernadt, 1993) suggested that only a small minority of patients

responds within one week. A recent meta-analysis reported that maximum benefit from lithium addition is attained after 7 days. In the present study, the early responders (i.e. within one week) constitute about one-third of the overall number of responders. With respect to the lithium dosing, there is again some controversy between studies reporting a good response on low plasma lithium levels, and others finding a superior response in patients with adequate lithium levels, as compared to samples with low lithium levels (Stein and Bernadt, 1993).

Chapter 4 reports on the double-blind comparison between two non-selective "classical" MAO inhibitors in antidepressant-refractory depressed patients.

Both MAO inhibitors showed a good response (about 45%) with no difference in efficacy between tranylcypromine and phenelzine. The overall drop-out rate in the present study was low (13%). In the literature more than 20 reports and case series addressed the use of MAOIs in treatment-resistant depression (Thase et al., 1995). In their comprehensive review, Thase et al. found that approximately 50% of TCA-resistant depressed patients respond to MAOIs (mainly tranylcypromine). Higher response rates of up to 70% are reported in subtypes of resistant bipolar depression (Thase et al., 1992). Phenelzine was studied mainly in so-called atypical depression. Atypical depression refers to depression with preserved mood reactivity and at least two additional atypical symptoms (increased appetite, increased sleeping time, weight gain, leaden feeling).

Phenelzine appeared to be effective both in atypical depression and in TCA-refractory atypical depression (Quitkin et al., 1993). Since treatment with tranylcypromine frequently leads to severe side-effects (such as agitation, insomnia and orthostatic hypotension) there clearly is a need for an MAO inhibitor, which is effective in TCA-refractory depression and is better tolerated than tranylcypromine.

Brofaromine, a reversible inhibitor of MAO-A seemed a useful alternative (Nolen et al., 1993), but it was withdrawn from further development by the pharmaceutical company. Moclobemide, another MAO-A inhibitor, is scarcely studied in antidepressant-refractory depression. The lingering clinical impression of several investigators is that there is no major role for moclobemide in refractory depression (Thase et al., 1995).

Since tranylcypromine and phenelzine are both chemically and pharmacologically different agents, a double-blind comparison was considered appropriate to assess whether phenelzine could be a useful alternative in refractory depression. Although there was no significant difference in drop-out rate and the emergence of severe

side-effects, our results did suggest a slightly better tolerability for phenelzine as compared with tranylcypromine.

Since the present study had a flexible-dose design, one would expect non-responders to receive a high (80-100 mg) dose of the MAOI, unless side-effects prevented dose increment.

In nonresponders the mean daily dose was significantly higher in the sample using phenelzine as compared with tranylcypromine. Our conclusion is that phenelzine is a useful alternative for tranylcypromine in antidepressant-refractory depression.

Chapter 5 describes how our routine administration of an esmolol bolus before anesthesia reduced the heart rate, mean arterial pressure and systolic blood pressure before the electrical stimulus. The increase in these variables during the convulsion was significantly less compared to placebo.

However, the seizure duration was also significantly reduced, which could make ECT less effective. Therefore, routine administration of esmolol is not advisable. During electrical-induced seizures cerebral blood flow, glucose and oxygen consumption increases markedly (Ackermann et al., 1986; Siesjo et al., 1986). The hemodynamic change associated with ECT is about 200-300%. Autoregulation of cerebral blood flow is not maintained during the seizure of ECT (Saito et al., 1996; Saito et al., 1995). The increased cardiac output and peripheral hypertension associated with the seizure may be necessary to sustain the profound ictal increase in cerebral blood flow. The enhanced cerebral blood flow provides the transport of oxygen and glucose that are necessary to sustain the large ictal increase in cerebral metabolic rate. Hypothetically limiting the peripheral hemodynamic surge may reduce the supply of oxygen and glucose to the brain. This could account for the reduced seizure duration with the use of β-blockers (Howie et al., 1990; Kovac et al., 1991; McCall et al., 1991; O'Flaherty et al., 1992).

The use of esmolol in patients with preexisting cardiac illness has not been well investigated and the following considerations should be kept in mind. Asystole during ECT can be an unintended side-effect of administering β-blockers. The application of the electrical stimulus results in vagal stimulation regardless of whether a seizure is induced. This parasympathetic discharge is prevented with the use of anticholinergic agents such as atropine or glycopyrrolate (McCall et al., 1994).

During or after the seizure, reflex bradycardia may occur; medication such as β-blockers can exaggerate post-seizure reflex bradycardia. For various reasons, subconvulsive stimulation can occur during ECT. In this case the parasympathic

discharge is unopposed, and in the presence of β-blockers asystole may result (Decina et al., 1984; McCall, 1996).

Secondly, patients with baseline tachycardia or hypertension showed the smallest absolute increase after seizure induction (Prudic et al., 1987; Webb et al., 1990). This may be due to the fact that sympathetic discharge may occur with pre-ECT anxiety, and ceiling effects limit further sympathetic activity with seizure induction. Thus the patient group we are studying might benefit less from the use of β-blockers.

The use of β-blockers should be reserved for patients who have an increased risk for vascular complications such as unstable aneurysms. An attempt should always be made to stabilize cardiovascular conditions as much as possible before the ECT course. In most patients with or without preexisting cardiac illness most practitioners will generally closely monitor cardiovascular changes during the initial treatments and treat cardiovascular complications acutely. Prophylaxis is considered for subsequent treatments. Most patients with serious cardiac illness will successfully complete an ECT course (Webb et al., 1990).

Chapter 6 presents a study on the use alfentanil during anesthesia for ECT. Alfentanil significantly reduced heart rate, diastolic arterial blood pressure and mean arterial pressure both before and after the stimulus. The increase in these variables during the convulsion was not affected, compared with placebo and after the stimulus all were significantly less compared to placebo. This effect can be attributed to an attenuating effect of the catecholamine release due to the stress of the procedure. Alfentanil does not lengthen seizure duration but does prolong apnea by about one minute in the dosage we used. Compared to the use of esmolol, alfentanyi has some advantages but the drug of choice with patients with preexisting cardiac illness is esmolol because of its greater effect and direct action on the cardiovascular system. Alfentanil could be an additional therapy to this. Higher doses of alfentanil would prolong apnea for too long.

Chapter 7 explores the relation between the presence of delusions and the efficacy of ECT. The present study is a post-hoc analysis of 55 depressed patients treated with ECT. The efficacy of ECT was higher in patients with delusional depression than in the non-deluded patients, with respect to both response and remission. Previous studies were not unanimous on this point. Some have reported a superior response to ECT in delusional depressives (Avery and Lubrano, 1979; Buchan et al., 1992), while others failed to find a difference (Kindler et al., 1991; Rich et al., 1986; Sobin et al., 1996; Solan et al., 1988). A number of factors may explain these

contradictory results. The administration of a low to moderate dose unilateral (ineffective) ECT in some studies may have reduced response in delusional patients more than in patients without delusions. The same consideration applies to the concomitant use of benzodiazepines. The concurrent use of antidepressants in some of the earlier studies may have improved the response in non-delusional patients, but less so in delusional depressed patients. Response to aspecific treatment factors, rather than "true" ECT response, is estimated to be substantial (30-40%) in non-delusional depression, whereas it is very low (0-10%) in delusional depression (Schatzberg and Rothschild, 1992). This placebo response in non-delusional depression might be enhanced by the use of concomitant psychotropic medication or ineffective ECT.

Moreover, it is unclear whether patients with mood–incongruent delusions were included in some of the previous studies, since the qualification of mood-congruence is mentioned in only one study (Sobin et al., 1996). The possibility, that the superior response in delusional depression is caused by a different factor, e.g. an overrepresentation of patients with melancholic features in the deluded sample, cannot be refuted.

Chapter 8 concerns a naturalistic one-year follow-up study of patients that had responded to ECT. The predictive value of adequate pre-ECT pharmacotherapy and the presence of delusions in relation to post-ECT relapse were assessed. Relapse rate for the whole sample was 28% after 6 months and 40% after 12 months. No relation between relapse rate at 6 and 12 months post-ECT and adequate pre-ECT pharmacotherapy was found, possibly because the sample without treatment resistance was too small. Both 6- and 12-month post-ECT relapse was significantly lower in patients with delusional depression compared with non-delusional patients. This finding is contradictory to the results of some previous studies (Aronson et al., 1987; O'Leary and Lee, 1996; Sackeim et al., 1990); however, these studies did not include a non-delusional control group. Only one of the previous studies reported a lower relapse rate in delusional depressives (Sackeim et al., 2001). The lower relapse rate in patients with delusional depression cannot be explained by a greater number of patients achieving remission directly post-ECT, since the mean HRSD score at the end of the ECT course was the same in both samples and very near total remission. Assuming that there were more placebo responders to ECT in the non-delusional sample, this could explain the higher relapse rate in patients with non-delusional depression, since placebo responders are more likely to relapse than "true" ECT responders. A large majority in both samples had suffered from depression

with melancholic features, so their presence could not account for the difference in relapse between both samples.

Even when patients were undergoing ECT because they had failed to respond to treatment with a TCA with adequate plasma levels for four weeks or an SSRI under the same conditions, followed by adding lithium and a non-reversible MAO inhibitor, relapse prevention with imipramine after response on ECT is still very effective.

Chapter 9 describes a trial which also showed that optimal results with ECT should be achieved in order to prevent relapse as much as possible.

ECT is one of the rare treatments in psychiatry which is discontinued after remission or response. In the case of a major depressive disorder responding to an antidepressant, that same medication is usually continued to prevent relapse. Continuation treatment is defined as the provision of somatic treatment during the 6-month period after the onset of remission in an index episode of mental illness. Because patients referred for ECT are usually medication-resistant, the choice of medication for relapse prevention is a difficult one. After ECT aggressive continuation therapy is in order because patients usually have a long duration of the index episode and are medication-resistant. Institution of continuation pharmacotherapy should be performed as soon as possible. From our own and previous research one can state that continuation therapy after successful ECT with placebo results in 80% relapse (Sackeim et al., 2001). From our results one can conclude that monotherapy with imipramine with adequate plasma levels prevents relapse in 80% of patients. This is in contrast to earlier studies which included, in our opinion less medication-resistant patients (Flint and Rifat, 1997; Sackeim et al., 2001). Relapse prevention with nortryptiline monotherapy succeeded in 40% of the patients. One could argue that imipramine (being a reuptake inhibitor of both serotonin and noradrenaline) may be more effective than nortryptiline (which is only a noradrenergic reuptake inhibitor) due to the difference in their pharmacodynamic profile.

The combination of nortriptyline and lithium prevented relapse in 60% of patients in the study by Sackeim et al. (2001), which is comparable to our results. Since the protective effect of lithium following ECT in unipolar patients is doubtful, it seems that the advantage of the combination with nortriptyline was due to synergistic or additive effects rather than an effect of lithium alone (Abou-Saleh, 1987; Coppen et al., 1981).

Obviously we need to adress the question which continuation therapy is best,

imipramine monotherapy or a combination of nortriptyline and lithium. A problem with the latter is the risk of more side-effects and the lower tolerability associated with combinations of drugs. Suggestions for an alternative strategy, such as tapering the frequency of ECT after remission while starting the continuation therapy during the weeks of tapering, is in our opinion elegant but premature.

Even some patients complying with the above-mentioned regimens relapse, which has led to the recommendation of continuation ECT for selected individuals (Decina et al., 1987; Jaffe et al., 1990; Kramer, 1987). However, data on continuation ECT are limited to retrospective series in patients with a depressive disorder.

Clinical implications

The results of our trial apply to depressed inpatients only. These patients are generally characterized by suicidality, melancholic and psychotic features, and a long duration of illness. After admission they should be treated with a TCA with the dose adjusted to therapeutic blood levels.

These trial results can not be applied to bipolar depressed patients. These patients were excluded from this study because recommendations for the treatment of acute bipolar depression are different (Nolen and Bloemkolk, 2000).

This is the second study comparing two antidepressant-lithium strategies (Bruijn et al., 1998), both favoring the imipramine strategy. Lithium addition is very effective for inpatients not responding to a TCA, therefore, the second step should be lithium addition for unipolar depressed inpatients.

Again, tranylcypromine was effective in nearly 50% of inpatients with refractory depression, confirming its place in the algorithm. Phenelzine may be a suitable alternative but replication studies are needed. Switching to phenelzine is indicated if patients can not tolerate low doses of tranylcypromine.

The results of our trial with esmolol bolus compared to placebo during ECT are contigent on a good working relationship with the anesthetist. Decisions have to be made about whether or not to use prophylactic pharmacological modifications for patients at increased cardiovascular risk. In patients with unstable hypertension and other unstable cardiac conditions an attempt should be made to stabilize the medical condition before beginning ECT. Because these prophylactic pharmacological modifications of the cardiovascular response to ECT have their own risks, judgment is needed about when to use such strategies.

The use of alfentanil in high-risk patients as part of the anesthesiafor ECT could

be considered.

Based on our finding that higher HRSD values after the end of the ECT course (even though remission or response is obtained) predicts relapse at six months follow-up, we encourage optimal ECT. To maximize response on ECT as much as possible one can not accept non response without having fully explored bilateral electrode placement. We think that at least 10 bilateral treatments should be given before one should accept the lack of response, unless the patient is intolerant to or refuses ECT. Increasing stimulus intensity should be considered. Medication with anticonvulsant properties, including anesthetic agents, should be avoided or minimized as much as possible. Based on our results and previous studies on continuation pharmacotherapy after successful ECT, it is not possible to make a clear statement about which drug or combination of drugs to reinstitute in the case of medication-resistant patients. It is advisable to start as quickly as possble with an antidepressant (preferably a TCA) with dose adjustment to plasma levels. Addition of lithium is an option, especially when this combination was of some benefit before ECT.

Recommendations for future research

In our opinion the efficacy of TCAs in depressed inpatients has been sufficiently well studied to favor the treatment of these patients with TCAs. If more reliable therapeutic plasma levels for SSRIs are discovered, another comparison with TCAs should be made. Further research with inpatients should involve antidepressants with pharmacological properties similar to TCAs, e.g. venlafaxine with dose adjustment to plasma level.

Comparison between TCAs and SSRIs with a methodology similar to that used in this trial could be of interest in outpatients. Trials comparing TCAs and SSRIs in outpatients found no differences in efficacy. This might also be due to the lack of discriminative power of the trials which could be enhanced by dose adjustment to plasma levels, low drop-out rate and minimal concurrent psychopharmacological medication.

Since the study comparing lithium addition to a TCA and an SSRI is the first such study, replication is warranted. Furthermore if a double-blind comparison between venlafaxine and a TCA is planned, lithium addition for non-remitters is considered useful.

Replication of the comparison between tranylcypromine and phenelzine in antidepressant-refractory depression is warranted, but it is doubtful whether it is

possible to include the number of patients needed to detect a modest difference between both MAOIs. Lithium addition to tranylcypromine is another interesting topic which has not yet been studied.

The idea that the frequency or severity of arrhythmias, cardiac ischemia and other cardiovascular events are reduced by minimizing the ECT-induced increases in heart rate and blood pressure has not yet been thoroughly investigated. The use of β-blockers has mainly been tested in healthy subjects. Whether the use of β-blockers is effective in limiting cardiovascular morbidity is of major importance for the use of this medication in patients at risk. Research with β-blockers during ECT should focus on patients with cardiovascular disease. It is of importance whether the effects are similar and of the same magnitude in this patient group.

The use of alfentanil to reduce hemodynamic changes due to the elicited seizure is limited. Newer short-acting opioids (e.g. remifentanyl) should be investigated for their effects on cardiovascular variables and seizure duration.

Treatment after successful ECT for a medication-resistant depressive disorder should at least consist of a tricyclic antidepressant. Further research is necessary to the question whether other relapse prevention strategies e.g. the tapering of ECT, instead of discontinuing abruptly and combining ECT with antidepressant during the ECT course are better alternatives.

In our opinion relapse prevention should also focus on the ability to cope with stressors, reorganization of social and vocational activities, and encouragement to return to a normal life and resolve residual symptoms. Medication-resistant depressed patients are often ill for a long time and may also have been hospitalized for a long period. There are no data on relapse prevention after successful ECT with other treatment modalities indicating which patients might benefit from such interventions, which is an omission in the treatment of these patients.

References

Abou-Saleh MT (1987). How long should drug therapy for depression be maintained? *American Journal of Psychiatry* 144:247-1248.

Ackermann RF, Engel J Jr, Baxter L (1986). Positron emission tomography and autoradiographic studies of glucose utilization following electroconvulsive seizures in humans and rats. *Annuals of the New York Academy of Sciences* 462:263-269.

Anderson IM (2000). Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. *Journal of Affective Disorders* 58:19-36.

Aronson TA, Shukla S, Hoff A (1987). Continuation therapy after ECT for delusional depression: a naturalistic study of prophylactic treatments and relapse. *Convulsive Therapy* 3:251-259.

Avery D, Lubrano A (1979). Depression treated with imipramine and ECT: the DeCarolis study reconsidered. *American Journal of Psychiatry* 136:559-562.

Bauer M, Dopfmer S (1999). Lithium augmentation in treatment-resistant depression: meta-analysis of placebo-controlled studies. *Journal of Clinical Psychopharmacology* 19:427-434.

Baumann P, Nil R, Souche A, Montaldi S, Baettig D, Lambert S, Uehlinger C, Kasas A, Amey M, Jonzier-Perey M (1996). A double-blind, placebo-controlled study of citalopram with and without lithium in the treatment of therapy-resistant depressive patients: a clinical, pharmacokinetic, and pharmacogenetic investigation. *Journal of Clinical Psychopharmacoly* 16:307-314.

Bruijn JA, Moleman P, Mulder PG, Van den Broek WW (1998). Comparison of two treatment strategies for depressed inpatients: imipramine and lithium addition or mirtazapine and lithium addition. *Journal of Clinical Psychiatry* 59:657-663.

Bruijn JA, Moleman P, Mulder PG, Van den Broek WW, Van Hulst AM, Van der Mast RC, Van de Wetering BJ (1996). A double-blind, fixed blood-level study comparing mirtazapine with imipramine in depressed in-patients. *Psychopharmacology* 127:231-237.

Buchan H, Johnstone E, McPherson K, Palmer RL, Crow TJ, Brandon S (1992). Who benefits from electroconvulsive therapy? Combined results of the Leicester and Northwick Park trials. *British Journal of Psychiatry* 160:355-359.

Coppen A, Abou-Saleh MT, Milln P, Bailey J, Metcalfe M, Burns BH, Armond A (1981). Lithium continuation therapy following electroconvulsive therapy. *British Journal of Psychiatry* 139:284-287.

De Groot P (1995). Consensus depressie bij volwassenen. *Nederlands Tijdschrift voor Geneeskunde* 139:1237-1241.

De Montigny C, Grunberg F, Mayer A, Deschenes JP (1981). Lithium induces rapid relief of depression in tricyclic antidepressant drug non-responders. *British Journal of Psychiatry* 138:252-256.

Decina P, Guthrie EB, Sackeim HA, Kahn D, Malitz S (1987). Continuation ECT in the management of relapses of major affective episodes. *Acta Psychiatrica Scandinavica* 75:559-562.

Decina P, Malitz S, Sackeim HA, Holzer J, Yudofsky S (1984). Cardiac arrest during ECT modified by beta-adrenergic blockade. *American Journal of Psychiatry* 141:298-300.

DeVane CL, Gill HS (1997). Clinical pharmacokinetics of fluvoxamine: applications to dosage regimen design. *Journal of Clinical Psychiatry* 58 (Suppl 5): 7-14.

Flint AJ, Rifat SL (1997). The effect of treatment on the two-year course of late-life depression. *British Journal of Psychiatry* 170:268-272.

Foglia JP, Perel JM, Nathan RS, Pollock BG, Lin FC, Nerayanan S (1990). Therapeutic Drug Monitoring (TDM) of fluvoxamine, a selective antidepressant. *Clinical Chemistry* 36:1043.

Glassman AH, Perel JM, Shostak M, Kantor SJ, Fleiss JL (1977). Clinical implications of imipramine plasma levels for depressive illness. *Archives of General Psychiatry* 34:97-204.

Howie MB, Black HA, Zvara D, McSweeney TD, Martin DJ, Coffman JA (1990). Esmolol reduces autonomic hypersensitivity and length of seizures induced by electroconvulsive therapy. *Anesthesia Analgesia* 71:384-388.

Jaffe R, Dubin W, Shoyer B, Roemer R, Sharon D, Lipschutz L (1990). Outpatient electroconvulsive therapy: efficacy and safety. *Convulsive Therapy* 6:231-238.

Katona CL (1995). Refractory depression: a review with particular reference to the use of lithium augmentation. *European Neuropsychopharmacology* 5(Suppl):109-113.

Katona CL, Abou-Saleh MT, Harrison DA, Nairac BA, Edwards DR, Lock T, Burns RA, Robertson MM. (1995). Placebo-controlled trial of lithium augmentation of fluoxetine and lofepramine. *British Journal of Psychiatry* 166:80-86.

Keller MB, Klerman GL, Lavori PW, Coryell W, Endicott J, Taylor J (1984). Long-term outcome of episodes of major depression. Clinical and public health significance. *Journal of the American Medical Association* 252:788-792.

Kindler S, Shapira B, Hadjez J, Abramowitz M, Brom D, Lerer B (1991). Factors influencing response to bilateral electroconvulsive therapy in major depression. *Convulsive Therapy* 7:245-254.

Kovac AL, Goto H, Pardo MP, Arakawa K. (1991). Comparison of two esmolol bolus doses on the haemodynamic response and seizure duration during electroconvulsive therapy. *Canadian Journal of Anaesthesiology* 38:204-209.

Kramer BA (1987). Maintenance ECT: A Survey of Practice (1986). *Convulsive Therapy* 3:260-268.

McCall WV (1996). Asystole in electroconvulsive therapy: Report of four cases. *Journal of Clinical Psychiatry* 57:199-203.

McCall WV, Reid S, Ford M (1994). Electrocardiographic and cardiovascular effects of subconvulsive stimulation during titrated right unilateral ECT. *Convulsive Therapy* 10:25-33.

McCall WV, Shelp FE, Weiner RD, Austin S, Harrill A (1991). Effects of labetalol on hemodynamics and seizure duration during ECT. *Convulsive Therapy* 7:5-14.

Moleman P, Bruijn JA, Tulen JHM. (1996). Het nut van bepaling van bloedspiegels van antidepressiva in de klinische praktijk. *Tijdschrift voor Psychiatrie* 38:16-19.

Nolen WA, Bloemkolk D (2000). Treatment of bipolar depression, a review of the literature and a suggestion for an algorithm. *Neuropsychobiology* 42 (Suppl 1): 11-17.

Nolen WA, Haffmans JPM, Bouvy PF, Duivenvoorden HJ (1993). Monoamine oxydase inhibitors in resistant major depression. A double blind comparison of brofaromine and tranylcypromine in patients resistant to tricyclic antidepressants. *Journal of Affective Disorders* 28:189-197.

O'Flaherty D, Husain MM, Moore M, Wolff TR, Sills S, Giesecke AH (1992). Circulatory responses during electroconvulsive therapy. The comparative effects of placebo, esmolol and nitroglycerin. *Anaesthesia* 47:563-567.

O'Leary DA, Lee AS (1996). Seven year prognosis in depression. Mortality and readmission risk in the Nottingham ECT cohort. *British Journal of Psychiatry* 169:423-429.

Paykel ES, Ramana R, Cooper Z, Hayhurst H, Kerr J, Barocka A (1995). Residual symptoms after partial remission: an important outcome in depression. *Psychological Medicine* 25:1171-1180.

Prudic J, Sackeim HA, Decina P, Hopkins N, Ross FR, Malitz S (1987). Acute effects of ECT on cardiovascular functioning: relations to patient and treatment variables. *Acta Psychiatrica Scandinavica* 75:344-351.

Quitkin FM, Stewart JW, McGrath PJ, Tricamo E, Rabkin JG, Ocepek-Welikson K, Nunes E, Harrison W, Klein DF (1993). Columbia atypical depression. A subgroup of depressives with better response to MAOI than to tricyclic antidepressants or placebo. *British Journal of Psychiatry* 166 (Suppl): 30-34.

Rasmussen BB, Brosen K (2000). Is therapeutic drug monitoring a case for optimizing clinical outcome and avoiding interactions of the selective serotonin reuptake inhibitors? *Therapeutic Drug Monitoring* 22:143-154.

Reisby N, Gram LF, Bech P, Nagy A, Petersen GO, Ortmann J, Ibsen I, Dencker SJ, Jacobsen O, Krautwald O, Sondergaard I, Christiansen J (1977). Imipramine: clinical effects and pharmacokinetic variability. *Psychopharmacology* 54:263-272.

Rich CL, Spiker DG, Jewell SW, Neil JF, Phillipson M (1986). ECT response in psychotic versus nonpsychotic unipolar depressives. *Journal of Clinical Psychiatry* 47:123-125.

Sackeim HA, Haskett RF, Mulsant BH, Thase ME, Mann JJ, Pettinati HM, Greenberg RM, Crowe RR, Cooper TB, Prudic J (2001). Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. *Journal of the American Medical Association* 285:1299-1307.

Sackeim HA, Prudic J, Devanand DP, Decina P, Kerr B, Malitz S (1990). The impact of medication resistance and continuation pharmacotherapy on relapse following response to electroconvulsive therapy in major depression. *Journal of Clinical Psychopharmacology* 10:96-104.

Saito S, Miyoshi S, Yoshikawa D, Shimada H, Morita T, Kitani Y (1996). Regional cerebral oxygen saturation during electroconvulsive therapy: monitoring by near-infrared spectrophotometry. *Anesthesia Analgesia* 83:726-730.

Saito S, Yoshikawa D, Nishihara F, Morita T, Kitani Y, Amaya T, Fujita T (1995). The cerebral hemodynamic response to electrically induced seizures in man. *Brain Research* 673:93-100.

Siesjo BK, Ingvar M, Wieloch T (1986). Cellular and molecular events underlying epileptic brain damage. *Annual of the New York Academic Sciences* 462:207-223.

Sobin C, Prudic J, Devanand DP, Nobler MS, Sackeim HA. (1996). Who responds to electroconvulsive therapy? A comparison of effective and ineffective forms of treatment. *British Journal of Psychiatry* 169:322-328.

Solan WJ, Khan A, Avery DH, Cohen S (1988). Psychotic and nonpsychotic depression: comparison of response to ECT. *Journal of Clinical Psychiatry* 49:97-99.

Stein G, Bernadt M (1993). Lithium augmentation therapy in tricyclic-resistant depression. A controlled trial using lithium in low and normal doses. *British Journal of Psychiatry* 162:634-640.

Thase ME, Mallinger AG, McKnight D, Himmelhoch JM. (1992). Treatment of imipramine-resistant recurrent depression, IV: A double-blind crossover study of tranylcypromine for anergic bipolar depression. *American Journal of Psychiatry* 149:195-198.

Thase ME, Trivedi MH, Rush AJ (1995). MAOIs in the contemporary treatment of depression. *Neuropsychopharmacology* 12:185-219.

Walczak DD, Apter JT, Halikas JA, Borison RL, Carman JS, Post GL, Patrick R, Cohn JB, Cunningham LA, Rittberg B, Preskorn SH, Kang JS, Wilcox CS (1996). The oral dose-effect relationship for fluvoxamine: a fixed-dose comparison against placebo in depressed outpatients. *Annual of Clinical Psychiatry* 8:139-151.

Webb MC, Coffey CE, Saunders WR, Cress MM, Weiner RD, Sibert TR (1990). Cardiovascular response to unilateral electroconvulsive therapy. *Biological Psychiatry* 28:758-766.

Samenvatting (Summary in Dutch)

Samenvatting

De kern van dit proefschrift gaat over de medicamenteuze behandelingsstrategie van opgenomen patiënten met een depressieve stoornis. Het doel van het beschreven onderzoek was het optimaliseren van de verschillende behandelstappen van deze behandelingsstrategie, mede door verbetering van de indicatiestelling. Het behandelschema (algoritme) bestaat uit een aantal stappen. De eerste stap is een antidepressivum; als dat niet of onvoldoende effect heeft wordt hieraan lithium toegevoegd. Daarna wordt bij uitblijven van (voldoende) werkzaamheid alle medicamenten gestopt en wordt een klassieke monoamine oxidase remmer (MAO-remmer) geprobeerd. De laatste stap van het algoritme is electroconvulsietherapie (ECT).

In *hoofdstuk 1* worden de epidemiologie van depressie en karakteristieken van opgenomen depressieve patiënten beschreven. Vervolgens wordt het in Nederland algemeen gebruikelijke behandelschema volgens de Centraal Begeleidingsorgaan voor de Intercollegiale Toetsing (CBO) besproken. Het CBO zet zich in voor verbetering van de Gezondheidszorg. Zij hebben een voorbereidingswerkgroep bestaande uit verschillende belanghebbende binnen de medisch specialisten en geestelijke gezondheidszorg ondersteund tijdens het opstellen van stellingen rond de behandeling van volwassen depressieve patiënten. Deze 41 stellingen over "depressie bij volwassenen" zijn besproken in een consensusbijeenkomst. Het resultaat van de gevoerde discussie en het ingekomen commentaar is de CBO consensus depressie bij volwassenen. Dit schema bestaat uit de volgende stappen: een antidepressivum, toevoeging van lithium aan het antidepressivum, een monoamine oxidase remmer en electroconvulsietherapie.

Wij hebben aan elke behandelfase van dit CBO schema één of meer onderzoeksvragen verbonden waarvan de resultaten zijn beschreven in dit proefschrift. Daarnaast worden de resultaten besproken van vier onderzoeksvragen die betrekking hebben op specifieke aspecten van electroconvulsietherapie.

In *hoofdstuk 2* wordt de opzet van een dubbelblind gerandomiseerd onderzoek beschreven waarin fluvoxamine en imipramine met elkaar worden vergeleken. Fluvoxamine is een antidepressivum, de eerste selectieve serotonine heropname remmer (SSRI). Imipramine, een tricyclisch antidepressivum (TCA), is het oudste antidepressivum en wordt in onderzoek meestal als de standaard antidepressieve behandeling gebruikt. In dit onderzoek werden patiënten opgenomen met een DSM-IV diagnose "depressieve stoornis" en een ernstscore volgens de Hamilton Rating

Scale for Depression (HRSD, 17 item versie) van ≥ 17 ingesloten. Na een medicatievrije periode van minstens één week, waarin patiënten gedurende vier dagen placebo gebruikten, werden de 138 patiënten die niet waren verbeterd, behandeld met studiemedicatie. De beide antidepressiva werden gedoseerd op geleide van de bloedspiegel. De referentiewaarden van de plasmaspiegels van zowel fluvoxamine als imipramine waren tevoren vastgesteld. Na vier weken behandeling met adequate plasmaspiegels bleek imipramine volgens één primaire uitkomstmaat (een daling van 50 % of meer op de HRSD) niet, maar volgens de andere (CGIS=Clinical Global Improvement Scale) wel effectiever dan fluvoxamine. Deze resultaten worden besproken aan de hand van de literatuur op dit gebied.

In *hoofdstuk 3* wordt ingegaan op de vergelijking van twee behandelingsstrategieën voor opgenomen depressieve patiënten; imipramine (fase 1) gevolgd door lithiumadditie voor patiënten die onvoldoende verbeterd waren (fase 2) of fluvoxamine (fase 1) eveneens gevolgd door lithiumadditie voor patiënten die onvoldoende verbeterd waren (fase 2). Lithium wordt meestal gebruikt voor de behandeling van de bipolaire stoornis. Naast antimanische heeft lithium ook antidepressieve effecten, zeker bij toevoeging aan een antidepressivum. De lithium werd toegevoegd aan het antidepressivum (imipramine of fluvoxamine) dat dubbelblind werd gecontinueerd. De dosering van lithium werd zodanig aangepast dat een lithiumspiegel van 0.6 tot 1.0 mmol/l werd bereikt. Het effect van de behandeling werd wekelijks gemeten met de HRSD totdat de patiënt gedurende drie weken een therapeutische lithiumspiegel had. Een survivalanalyse van de totale patiëntengroep toonde aan dat significant meer patiënten in de behandelingsstrategie "imipramine gevolgd door lithium-additie" volledig herstelden.

In *hoofdstuk 4* worden de opzet en de resultaten van het dubbelblinde gerandomiseerde onderzoek met twee verschillende klassieke MAO-remmers beschreven. In dit onderzoek werden zevenenzeventig patiënten geïncludeerd en na een medicatievrije week behandeld werden met de MAO-remmer tranylcypromine of fenelzine. Drieëntwintig van deze patiënten waren zonder succes behandeld volgens één van de twee in het vorige hoofdstuk beschreven strategieën; de overige 54 patiënten waren zonder succes buiten het onderzoek adequaat behandeld met tenminste een tricyclisch antidepressivum in een andere kliniek. De duur van de dubbelblinde behandeling met één van beide MAO-remmers bedroeg vijf weken. Er werd gestart met een dosis van 20 mg per dag; als de patiënt onvoldoende verbeterd was kon de dagdosering twee keer per week worden verhoogd met 20 mg tot een maximale dosis van 100 mg per dag. Het effect van de behandeling werd wekelijks gemeten met de HRSD. Beide klassieke MAO-remmers bleken even effectief wat

betreft het aantal patiënten dat duidelijk verbeterde. De gemiddelde mate van verbetering was groter bij tranylcypromine, maar dit was statistisch niet significant.

Electroconvulsietherapie (ECT) is in het algoritme de volgende stap. ECT is een veilige en effectieve behandeling. Er bestaan geen absolute contra-indicaties voor deze behandeling. Tijdens de behandeling waarbij er een epileptische aanval wordt opgewekt met een kortdurende stroom, is er sprake van een kortdurende stijging van de bloeddruk en de hartfrequentie. Dit kan voor patiënten met hart- en vaatziekten risico's geven. De behandeling gebeurt onder narcose en met behulp van een spierverslappend middel, reden waarom patiënten tijdens de behandeling met een kapje beademd worden. Na de behandeling kunnen kortdurende verwardheid, spierpijn en hoofdpijn optreden.

In *hoofdstuk 5* wordt verslag gedaan van de resultaten van onderzoek naar de toepassing van esmolol bij ECT. Esmolol is een kortwerkende β-blokker die de toename van de bloeddruk en hartfrequentie tijdens ECT zou kunnen verminderen. Doel van dit onderzoek was om na te gaan of esmolol zonder bezwaren bij alle patiënten voor de ECT zou kunnen worden toegediend. Esmolol bleek in vergelijking met placebo inderdaad de waarden van de systolische bloeddruk, de gemiddelde arteriële bloeddruk en de hartfrequentie te verlagen zowel voor de toediening van de stroom (de stimulus) als tijdens het opgewekte insult. De duur van het insult wordt echter door esmolol verkort wat de effectiviteit van ECT kan verminderen. Om deze reden is het niet verstandig om bij alle patiënten die ECT ondergaan esmolol te geven, maar het gebruik ervan te beperken tot patiënten die een verhoogd risico hebben op complicaties door hart- en vaataandoeningen of die tijdens de behandeling te lang een te hoge bloeddruk en hartfrequentie blijven houden.

In *hoofdstuk 6* wordt het gebruik van het opiaat alfentanil tijdens de narcose voor ECT besproken. We onderzochten het effect van alfentanil op de bloeddruk en de hartfrequentie, op de duur van het insult, het effect op myocloniën als bijwerking van het narcose middel etomidate, de duur van de ademstilstand en op het optreden van verwardheid kort na ECT. Alfentanil heeft in vergelijking met placebo een significant gunstig effect zowel voor en na de stimulus toediening op hartfrequentie, diastolische bloeddruk en gemiddelde arteriële bloeddruk. De duur van het insult wordt niet beïnvloed. De ademstilstand duurt gemiddeld 73 seconden langer vergeleken met placebo. Alfentanil geeft niet meer verwardheid dan placebo noch heeft het een preventieve werking op het optreden van myocloniën als bijwerking van het narcosemiddel etomidate.

In *hoofdstuk 7* worden de resultaten beschreven van een retrospectief onderzoek

naar de effectiviteit van ECT bij depressieve patiënten met en zonder psychotische kenmerken. Alle patiënten die in de periode van 1993-2000 met een depressieve episode volgens de DSM-IIIR met ECT werden behandeld, werden in het onderzoek geïncludeerd. Patiënten die al eerder met ECT waren behandeld werden uitgesloten. Patiënten werden in de psychotische groep ingedeeld als zij duidelijk blijk gaven van stemmingscongruente wanen. Het merendeel van de patiënten (36/55, 65%) werd behandeld met bilaterale ECT. Bijna alle patiënten, op vijf na, waren medicatievrij tijdens de ECT kuur. Deze vijf patiënten kregen droperidol voorafgaand aan de ECT en drie van hen gebruikten ook haloperidol. Na de kuur bleek ECT uitermate effectief bij patiënten met stemmingscongruente wanen: 24 van de 26 patiënten (92%) verbeterde aanzienlijk. Het responspercentage in de niet-psychotische groep was veel lager, namelijk 16 van de 29 (55%). Van de psychotische depressieve patiënten herstelde 57% volledig, terwijl volledig herstel in de niet-psychotische groep slechts bij 24% optrad.

In *hoofdstuk 8* wordt verslag gedaan van onderzoek naar de effectiviteit van ECT op de lange termijn. Hiervoor werden 40 patiënten die aanzienlijk verbeterd waren tijdens behandeling met ECT gedurende één jaar gevolgd: het merendeel prospectief (n=28) en de overigen retrospectief (n=12). We onderzochten de voorspellende waarde van twee belangrijke ziektekenmerken, medicatieresistentie en psychotische kenmerken, voor een terugval naar depressie binnen één jaar. De 40 geïncludeerde patiënten hadden een depressieve episode volgens de DSM-IIIR criteria, een daling op de HRSD van minstens 50% gedurende de ECT kuur, en een HRSD score ≤ 14 bij het staken van de ECT. Medicatieresistentie werd vastgesteld met een daarvoor ontwikkeld meetinstrument, de Antidepressant Treatment History Form (ATHF). Criteria voor terugval waren: de noodzaak voor aanpassing van antidepressiva, heropname, of duidelijk slechter psychosociaal functioneren. Wij vonden geen relatie tussen medicatieresistentie enerzijds en terugval na ECT anderzijds, maar de groep patiënten die niet medicatieresistent was volgens de ATHF was erg klein. De terugval bleek aanmerkelijk groter in de groep patiënten die voorafgaand aan ECT geen psychotische kenmerken had, vergeleken met de patiënten die oorspronkelijk psychotisch depressief waren. Dit verschil werd zowel na zes als na twaalf maanden gevonden en bleek na twaalf maanden nog verder toegenomen.

Hoofdstuk 9 gaat over een dubbelblind placebogecontroleerd onderzoek naar voortgezette behandeling met imipramine na succesvolle ECT. Zevenentwintig patiënten die onvoldoende hadden gereageerd op een adequaat uitgevoerde behandeling met een tricyclisch antidepressivum of fluvoxamine werden in het onderzoek opgenomen. De meeste patiënten waren, behalve met antidepressiva, ook

nog met lithiumadditie en een klassieke MAO-remmer behandeld. Alle patiënten waren vervolgens duidelijk verbeterd door ECT (50% afname op de HRSD). Voor de voortgezette behandeling moesten patiënten bij instroom een score op de HRSD hebben van ten hoogste 16 punten. Voortgezette behandeling met imipramine na ECT gedurende zes maanden bleek effectief in het voorkomen van terugval. In de placebo-groep vielen twaalf van de 15 patiënten (80%) vergeleken met 2 van de 11 patiënten (18%) in de imipramine-groep. Verder bleek dat hoe hoger de HRSD was na de ECT, hoe groter de kans was op een terugval.

Hoofdstuk 10 bevat de samenvatting en discussie waarvan deze beknopte Nederlandse versie deel uitmaakt. De effectiviteit van het hele behandelschema wordt beschreven. Hoewel dit onderzoek niet bedoeld was om het behandelschema als geheel te onderzoeken maar de afzonderlijke stappen ervan, hebben we door het volgen van patiënten vanaf de eerste fase van het behandelschema een unieke kans het effect van de achtereenvolgende stappen hiervan voor deze patiënten te beschrijven. De uitkomst van het behandelschema werd geëvalueerd volgens 1) een vermindering van 50% op de HRSD en 2) een score van 7 of lager op de HRSD.

De uitkomst van beide criteria kunt u volgen in schema 1 en schema 2. Uiteindelijk was er bij 115 van de 138 patiënten (83%) sprake van een daling van 50% of meer op de HRSD en bij 84 van de 138 patiënten (61%) was er sprake van een HRSD score van 7 of lager.

Resumerend komen wij tot de volgende *conclusies.*

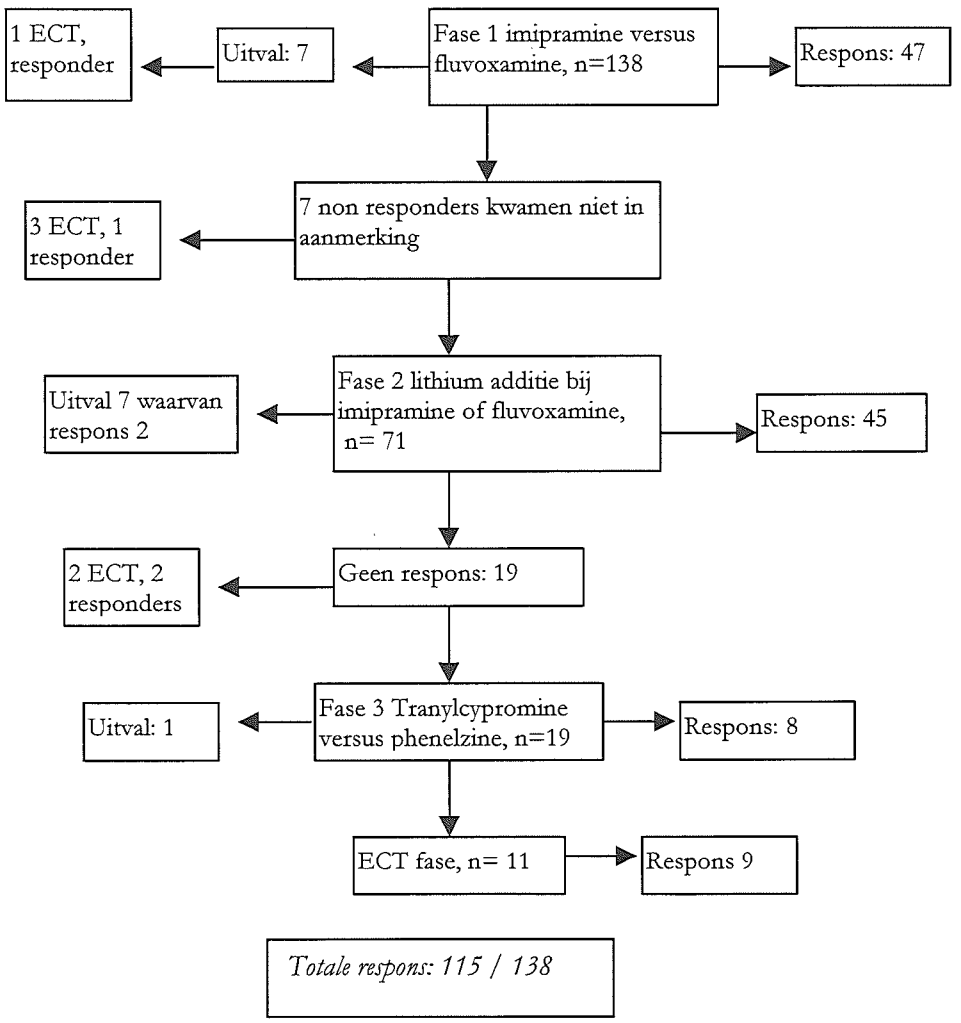
De resultaten van ons onderzoek hebben betrekking op opgenomen depressieve patiënten. De resultaten kunnen niet betrokken worden bij de behandeling van depressies in het kader van een bipolaire stoornis bij opgenomen patiënten.

Ons onderzoek bevestigt eens te meer, dat deze patiënten behandeld moeten worden met een TCA onder spiegelcontrole. De strategie van voorkeur bij geen of te weinig verbetering is de additie van lithium. Lithiumadditie is snel en effectief bij opgenomen depressieve patiënten en leidt bij met imipramine behandelde patiënten in 60% tot een volledig herstel. Tranylcypromine bleek bij 50% van de patiënten effectief, ondanks dat er al meerdere antidepressiva geprobeerd waren. De klassieke MAO-remmers hebben volgens ons een plaats in het behandelschema. Als patiënten tranylcypromine al bij lage doseringen niet kunnen verdragen dan bleek in dit onderzoek, dat fenelzine een volwaardig alternatief is.

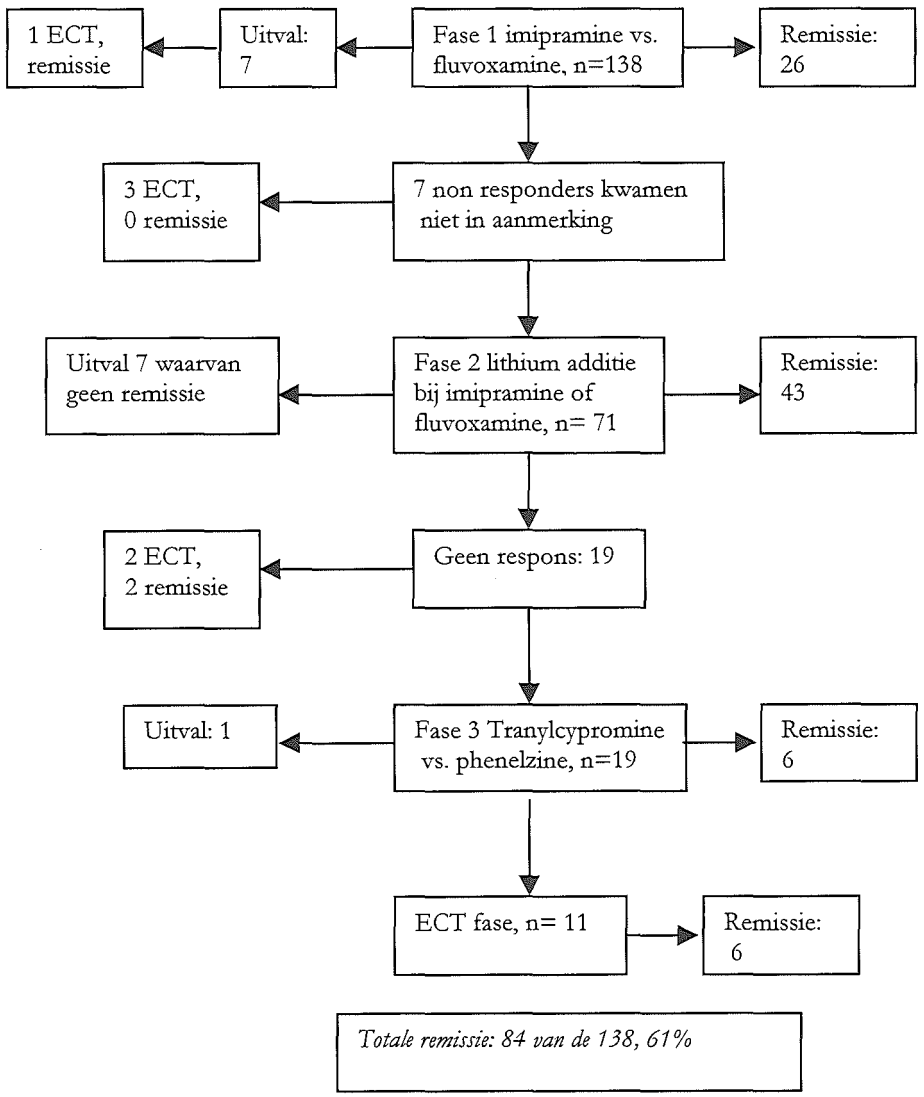
ECT bij patiënten met hart- en vaatziekten kan veiliger plaats vinden met het gebruik van esmolol bij te langdurige of te hoge bloeddruk en hartfrequentie. Alfentanil kan hierbij ook een optie zijn.

Zelfs bij depressieve patiënten met geen of weinig effect van meerdere antidepressiva moet ECT verricht worden. De ECT moet op optimale wijze toegediend worden en gericht zijn op een volledig herstel. Na herstel op ECT is zeker bij patiënten die niet of te weinig hebben gereageerd op antidepressiva voor de ECT een goede medicamenteuze nabehandeling essentieel. Deze nabehandeling dient minstens te bestaan uit een TCA met therapeutische bloedspiegels.

Schema 1. Respons, een vermindering van minstens 50% op de HRSD



Schema 2. Remissie, een score van 7 of lager op de HDRS



Referenties

Zie bij Summary and general discussion.

Dankwoord (acknowledgments)
Curriculum vitae
T.K. Birkenhäger

Dankwoord T.K. Birkenhäger

Ik wil alle *patiënten*, die deelgenomen hebben aan het onderzoek tijdens hun opname op de Biologisch-Psychiatrische afdeling (BPA) van voormalig Psychiatrisch Centrum Bloemendaal, hartelijk bedanken.

De *directie van Psychiatrisch Centrum Bloemendaal* (tegenwoordig: Parnassia) was bereid om het onderzoek financieel te ondersteunen en stelde mij in de gelegenheid om het onderzoek uit te voeren, ik wil *Ruud van Beest, Frits Verschoor en Leen Joele* hiervoor hartelijk bedanken.

Professor *Peter Moleman*, beste promotor, jij hebt het hele traject van de eerste versie van het protocol tot het schrijven van de afzonderlijke artikelen intensief en zeer deskundig begeleid. Ik hoop nog lange tijd met je te mogen samenwerken en van je te kunnen leren.

Professor *Michiel Hengeveld*, beste promotor, hoewel jij pas in een later stadium bij het onderzoek betrokken raakte, heb jij het schrijven van het manuscript op een prettige en faciliterende manier begeleid. Ik ben je hiervoor zeer erkentelijk. Ook dank ik je voor het zorgvuldig corrigeren van een aantal hoofdstukken van het manuscript en het schrijven van een indrukwekkend aantal brieven aan het bureau "Universitaire Plechtigheden".

Jan Bruijn, beste co-promotor, jij hebt ooit tijdens mijn opleiding mijn interesse gewekt voor de behandeling van depressie. Later heb je het hele traject vanaf het schrijven van het protocol met het voor jou kenmerkende enthousiasme en optimisme begeleid. Daarnaast heb je een deel van de metingen verricht, waarvoor ik je hartelijk dank.

Walter van den Broek, beste mede-promovendus, de samenwerking met jou is van meet af aan zeer prettig verlopen. Ik heb jouw steun op diverse manieren ervaren, niet in het minst wanneer er zich op computergebied problemen aandienden. Ja, ik zal met "endnote" leren werken (al is het ná de promotie)! Ik hoop dat we onze samenwerking nog lang op deze manier voort kunnen zetten.

Professor *Willem Nolen* en *Paul Bouvy* hebben mij destijds laten zien hoe interessant patiëntgebonden wetenschappelijk onderzoek kan zijn en mij later benaderd met de vraag of ik als psychiater op de BPA wilde werken.

De *promotiecommissie* wil ik bedanken voor het beoordelen van het manuscript.

Klinisch patiëntgebonden onderzoek staat of valt met de inzet van het *behandelteam*.

Ik wil *alle leden van het team van de BPA* van voormalig Psychiatrisch Centrum

Bloemendaal (tegenwoordig: de kliniek stemmingsstoornissen van Parnassia) heel hartelijk danken voor hun inzet. Dit onderzoek had niet succesvol kunnen worden uitgevoerd zonder hun inzet en enthousiasme voor het onderzoek van de verpleegkundigen, de vaktherapeuten, de afdelingsassistente en de maatschappelijk werker. Zij hebben de vaak ernstig depressieve patiënten tijdens de medicatie-afbouw, de medicatievrije observatie en de diverse onderzoeksfasen vakkundig begeleid. Ik wil hier de teamleden, die gedurende het hele onderzoek op de afdeling werkten noemen: *Judith Bolten, Mirjam Booms, Meertine Laansma, Walter Molenaar, Arthur Schipper, Marianne Schouten, Peter Smit, Lonneke van Vliet en Jos Zwennes*, ik ben jullie heel erkentelijk. *Jan Veenhoven*, zorgcoördinator èn onderzoeksverpleegkundige, eigenlijk zou jij vandaag ook moeten promoveren. Jij regelde de planning van het onderzoek, coachte andere verpleegkundigen en wist in mijn afwezigheid dreigende uitval te voorkomen. Ik heb het als een voorrecht ervaren om jaren met je samen te hebben kunnen werken (en nog iets: het is echt handig om het onderzoeksbord te gebruiken!).

Bij afwezigheid van Jan Veenhoven verving *Henry Burgers* hem op bekwame wijze.

De *arts-assistenten*, die gedurende het onderzoek op de BPA werkten hebben eveneens een belangrijke rol gespeeld bij de uitvoering van het onderzoek, zowel bij het motiveren van de patiënten als bij het uitvoeren van de metingen. Ik ben *Esther Pluijms, Jane Beck, Henriëtte Berger, Leon Heyting en Jan-Willem Renes* dankbaar voor hun betrokkenheid bij het onderzoek. *Wim Dijken* verbrak bij ontslag de medicatiecode van een groot aantal patiënten en was verantwoordelijk voor de nazorg van een aanzienlijk aantal van hen. *Wilma Winter* van de apotheek wil ik bedanken voor de zorgvuldige verstrekking van de studiemedicatie. De *medewerkers van het laboratorium*, van wie ik *Piet Sturm en Johan Bommelé* wil noemen, zorgden op nauwgezette wijze voor de afname van de plasmaspiegels en het verwerken van de bloedmonsters, waarvoor ik hen dank. *Judith Haffmans* wil ik bedanken voor de kundige wijze waarop zij mij ter zijde stond bij het indienen van het onderzoeksvoorstel bij de Medisch-ethische commissie. *Marja Kool* ben ik zeer erkentelijk voor de zorgvuldige invoer van de data.

Paul Mulder heeft op zeer deskundige wijze de statistische analyses begeleid en de complexere analyses uitgevoerd. Paul, ik bewonder je om je geduld, je vond het geen probleem om sommige zaken twee of drie keer uit te leggen. Verder was je altijd beschikbaar voor overleg. De database is op vakkundige wijze ontworpen *door Theo Broekman. Laraine Visser* bedank ik voor de vlotte en accurate correctie van het Engels. *Tini Zaanen* wil ik hartelijk bedanken voor het vervaardigen van de uiteindelijke versie van het manuscript.

Mijn paranimfen, *Rinus Vegt en Gunnar Faber*, bedank ik omdat ze mij vandaag terzijde willen staan. Rinus en Gunnar, de vriendschap met jullie is een waardevol gevolg van de basisopleiding psychiatrie. Ik hoop nog lang van jullie kritische en relativerende humor te mogen genieten. Lieve *Betty, Charlotte, Marius en Simone*, ik ben jullie dankbaar voor de steun en de afleiding die ik van jullie heb gekregen. Jullie hebben met succes verhinderd, dat ik thuis overdreven lang aan het werk was. Betty, je was betrokken, maar niet te en dat was prima voor mij. Het zou allemaal wel goed komen volgens jou, en dat is voor mij een grote steun geweest.

Curriculum vitae

Tom Birkenhäger werd geboren op 25 augustus 1959 te Amsterdam. In 1977 behaalde hij het Atheneum-B diploma aan het Montessori Lyceum te Rotterdam. In 1977 begon hij de studie geneeskunde aan de Erasmus Universiteit te Rotterdam. Het artsexamen werd behaald op 14 november 1984.

Vervolgens werkte hij als arts-assistent niet in opleiding op de afdelingen neurologie en psychiatrie van het Academisch Ziekenhuis Rotterdam-Dijkzigt (tegenwoordig: Erasmus MC). Van 1 juli 1986 tot 1 juli 1989 volgde hij de basisopleiding psychiatrie in het Academisch Ziekenhuis Rotterdam-Dijkzigt (opleider: prof.dr. W.J. Schudel). Zijn stage sociale psychiatrie volgde hij bij de RIAGG Centrum-West te Rotterdam (opleider: dr. R.E. Offerhaus). Zijn keuzejaar biologische psychiatrie in combinatie met wetenschappelijk onderzoek volgde hij in 1990-1991 op de Biologisch Psychiatrische Afdeling van het toenmalige Psychiatrisch Centrum Bloemendaal (opleider: prof.dr. W.A. Nolen). Hij werd ingeschreven in het specialisten register op 1 april 1991.

Van 1991 tot 1993 werkte hij als psychiater op de afdeling sociale psychiatrie van Riagg Rijnmond-Noordwest te Rotterdam. Van 1993 tot 2002 werkte hij als psychiater op de Biologisch Psychiatrische Afdeling van het toenmalige Psychiatrisch centrum Bloemendaal (tegenwoordig: Parnassia Psychomedisch Centrum). Op deze afdeling verrichte hij het onderzoek dat in dit proefschrift wordt beschreven. Van 2002 tot 2003 werkte hij op de afdeling stemmingsstoornissen van het Universitair Medisch Centrum te Utrecht (UMCU; hoofd: prof.dr. R.S. Kahn). Sinds 1 maart 2003 is hij werkzaam als psychiater op de zorglijn depressieve stoornissen van het Erasmus MC (hoofd: prof.dr. M.W. Hengeveld).

Hij is lid van de multidisciplinaire werkgroep voor de richtlijn Depressie van het CBO en van de Werkgroep Electroconvulsietherapie Nederland.

Hij is getrouwd met Betty Gillesse, samen hebben zij drie kinderen: Charlotte, Marius en Simone.

Publicaties van T.K. Birkenhäger

Vegt M, Birkenhäger TK, Van Hulst AM (1990). Hoe aspecifiek is de psychopathologie van primaire hersentumoren? *Tijdschrift voor Psychiatrie* 32:486-496.

Vegt M, Bruijn JA, Birkenhäger TK (1991). Het gebruik van schildklierhormoon bij de behandeling van depressies: Een literatuuroverzicht. *Acta Neuropsychiatrica* 3:17-21.

Birkenhäger TK, Bruijn JA, Nolen WA, Vegt M (1991). MAO-remmers als antidepressiva: een literatuuroverzicht betreffende indicatiegebied en werkingsmechanisme. *Tijdschrift voor Psychiatrie* 33:445-462.

Birkenhäger TK, Nolen WA, Moleman P (1992). Is er plaats voor benzodiazepines bij de farmacotherapie van depressie? *Tijdschrift voor Psychiatrie* 34:465-482.

Nolen WA, Birkenhäger TK, Moleman P (1992). Moclobemide, de eerste MAO-A remmer, echt iets nieuws? *Nederlands Tijdschrift voor Geneeskunde* 136: 1492-1496.

Birkenhäger TK, Nolen WA, Moleman P (1992). Hoofdstuk 2, Antidepressiva In: *Praktische psychofarmacologie,* 2e herziene druk. Moleman P (red). Bohn Stafleu Van Loghum, Houten, pp 49-123.

Birkenhäger TK, Vegt M (1994). Fenelzine: een vergeten MAO-remmer met een specifiek indicatiegebied. *Tijdschrift voor Psychiatrie* 36:182-194.

Gernaat HB, Haffmans PM, Knegtering H, Birkenhäger TK (1995). Tranylcypromine in narcolepsy. *Pharmacopsychiatry* 28:98-100.

Birkenhäger TK, Moleman P, Nolen WA (1995). Benzodiazepines for depression? *International Clinical Psychopharmacology* 10:181-195.

Leentjens AF, Van den Broek WW, Birkenhäger TK, Moleman P, Bruijn JA (1996). Het effect van medicamenteuze vervolgbehandeling na succesvolle electroconvulsietherapie is nog teleurstellend. *Nederlands Tijdschrift voor Geneeskunde* 140:241-243.

Birkenhäger TK, Vegt M, Nolen WA (1997). An open study of triiodothyronine augmentation of tricyclic antidepressants in inpatients with refractory depression. *Pharmacopsychiatry* 30:23-26.

Otte W, Van den Broek WW, Birkenhäger TK, Van de Wetering BJ (1997). Het serotonine syndroom. *Tijdschrift voor Psychiatrie* 39:388-399.

Birkenhäger TK, Moleman P (1998). Hoofdstuk 2, Antidepressiva In: *Praktische psychofarmacologie*, 3e herziene druk. Moleman P (red). Bohn Stafleu Van Loghum, Houten, pp 47-139.

Birkenhäger TK, Moleman P (1998). Hoofdstuk 6, Biologische therapievormen. In: *Behandelingsstrategieën bij depressie.* Nolen WA, CA Hoogduin (red). Bohn Stafleu Van Loghum, Houten, pp 60-84.

Birkenhäger TK (1998). De plaats van MAO-remmers bij de behandeling van depressie. *Cobo-bulletin* 31:26-29.

Birkenhäger TK, Verweij B (1999). Hoofdstuk 7, ECT en Psychofarmaca In: *Electroconvulsietherapie.* Broek WW van den, A.F. Leentjens, B. Verweij, red. Bohn Stafleu Van Loghum, Houten pp 53-60.

Birkenhäger TK, Moleman P (1999). Twee nieuwe antidepressiva: mirtazapine en velafaxine. *Nederlands Tijdschrift voor Geneeskunde* 143:934-937.

Birkenhäger TK (2000) Hoofdstuk 2, Opgenomen patiënten met een depressieve stoornis. In: *Behandeling met psychofarmaca: voorbeelden uit de dagelijkse praktijk.* Balkom AJ van, PN van Harten, P Kölling, P Moleman (red). Bohn Stafleu Van Loghum, Houten, pp 16-27.

Birkenhäger TK (2000). Therapieresistentie: Algemene Inleiding. *Cobo-bulletin* 33:3-4.

Melissen J, Pruissen A, Birkenhäger TK (2000). Voeding en lithium, een zaak van gewicht. *Voeding Nu* 2:21-23.

Pluijms EM, Birkenhäger TK, Huijbrechts IP, Moleman P (2002). Influence of resistance to antidepressant pharmacotherapy on short-term response to electroconvulsive therapy. *Journal of Affective Disorders* 69:93-99.

Beck-Lie A Fat JR, Birkenhäger TK, Renes JW (2002). Ontremming tijdens toevoeging van lithium bij depressie resistent tegen imipramine. *Nederlands Tijdschrift voor Geneeskunde* 146:2157-2160.

Birkenhäger TK, Van den Broek WW, Spijker J (2003). Hoofdstuk 5, Farmacotherapie bij chronische depressie en dysthymie. In: *Behandelingsstrategieën bij chronische depressie en dysthymie.* Blom MB, J Spijker, R van Dyck, red. Bohn Stafleu Van Loghum. Houten/Mechelen, pp 62-70.

Birkenhäger TK, Pluijms EM, Lucius SA (2003). ECT response in delusional versus nondelusional depressed inpatients. *Journal of Affective Disorders* 74:191-195.

Otte W, Birkenhäger TK, Van den Broek WW (2003). Fatal interaction between tranylcypromine and imipramine. *European Psychiatry* 18:264-265.

Birkenhäger TK, Van den Broek WW (2004). Nieuwe meta-analyse betreffende effectiviteit van ECT bij depressie: een bijdrage tot consensus? *Tijdschrift voor Psychiatrie* 46:54-55.

Birkenhäger TK, Renes JW, Pluijms EM (2004). One-year follow-up after successful ECT: a naturalistic study in depressed inpatients. *Journal of Clinical Psychiatry* 65:87-91.

Broek WW van den, Birkenhäger TK, Mulder PG, Bruijn JA, Moleman P (2004). A double-blind study comparing imipramine with fluvoxamine in depressed inpatients. *Psychopharmacology* (in press).

Birkenhäger TK, Van den Broek WW, Mulder PG, Bruijn JA, Moleman P (2004). A double-blind study of two two-phase treatments for depressed inpatients: imipramine versus fluvoxamine, both followed by lithium addition. *American Journal of Psychiatry* (in press).

Broek WW van den, de Lely A, Mulder PG, Birkenhäger TK, Bruijn JA (2004). Effect of medication resistance on short-term response to electroconvulsive therapy (ECT). *Journal of Clinical Psychopharmacology* (in press).

Dankwoord (acknowledgments)
Curriculum vitae
W.W. van den Broek

Dankwoord W.W. van den Broek.

Allereerst wil ik alle *patiënten* bedanken die, opgenomen op de afdeling psychiatrie van het Erasmus MC, meegedaan hebben aan dit onderzoek. Hun medewerking en vertrouwen werd ook mogelijk gemaakt door het *behandelteam van de unit* waar dit onderzoek plaatsvond. Het is vooral door de inzet en expertise van de *verpleegkundigen, arts-assistenten, vaktherapeuten, maatschappelijk werkenden en psychologen* dat dit onderzoek tot een goed einde is gekomen. De *verpleegkundigen* wil ik nog eens speciaal noemen. Hoewel het de afgelopen jaren niet altijd even makkelijk was, hebben jullie loyaal aan dit onderzoek meegewerkt. Ik ben er trots op met jullie te mogen samenwerken.

Jan Bruijn, mijn copromotor, jij was het die de grondbeginselen van dit onderzoek op de afdeling hebt geïmplementeerd. Jij hebt de "depressieafdeling" opgericht en gemaakt tot een echte onderzoeksafdeling. Ik voel het nog steeds als een voorrecht dat ik je mocht opvolgen. Ik hoop nog lang van onze wetenschappelijke en minder wetenschappelijke discussies te mogen genieten.

Professor *Michiel Hengeveld*, jij hebt de afdeling in een moeilijke fase overgenomen en kwam pas in de laatste fase van het onderzoek en onze promotie in beeld. Ik heb je begeleiding tijdens dit stadium zeer gewaardeerd, je hebt me op een directe, pragmatische, betrokken kortom heel prettige manier begeleid. Je hebt het manuscript op taal beoordeeld. Voor dit alles mijn hartelijke dank.

Professor *Peter Moleman*, jij stond samen met Jan Bruijn aan de wieg van dit onderzoek. Je wetenschappelijke attitude is voor mij altijd een belangrijk voorbeeld geweest. Je inbreng in de manuscripten waren een waardevolle aanvulling. Ik heb genoten van onze discussies over dit onderzoek en ik hoop dat ik bij de verdere bewerking van de gegevens van dit onderzoek van je grote deskundigheid en wetenschappelijke interesse gebruik mag blijven maken.

Professor *Willem Nolen*, jij was de eerste in Nederland die op een soortgelijk onderwerp promoveerde. Ik herinner me nog dat dit op mij, jonge assistent, veel indruk maakte. Ondertussen zijn we vrienden geworden en delen we ook andere interesses.

Beste *Tom Birkenhäger*, mijn mede promovendus, wij kennen elkaar al vanaf onze opleiding. De paden van onze carrières hebben elkaar regelmatig gekruist. Onze samenwerking heb ik altijd als zeer plezierig ervaren. Ik hoop dat we nog vele jaren van elkaars enthousiasme en humor mogen genieten en dat onze samenwerking nog lang zijn vruchten zal afwerpen, samen met onze nieuwe collega *Esther Pluijms*.

Professor *Jan Klein* dank ik voor de bereidwilligheid als anesthesist een psychiatrische promotie te beoordelen. De promotie-commissie dank ik voor het beoordelen van het proefschrift.

Paul Mulder, jij was bereid de statistische bewerking van de gegevens te begeleiden. Jij bent de eerste statisticus die ik ken die een dokter ingewikkelde analyses zo kan uitleggen dat hij het ook nog begrijpt. Het feit dat het niet lang blijft "hangen" heeft te maken met mijn dagelijks werk dat andere kwaliteiten van mij vraagt. Ik heb veel waardering voor de geduldige manier waarop je mij hebt begeleid en respect voor de zuivere en wetenschappelijk verantwoorde wijze waarop je statistische technieken toepast. Ik hoop nog vaak van je kennis en vrolijke gezelschap gebruik te mogen maken.

Paul Bouvy, je was betrokken bij het begin van het onderzoek. De gezellige discussies met jou hebben mede bijgedragen aan dit onderzoek, waarvoor mijn dank.

Siska Verploegh heeft er voor gezorgd dat alles op juiste wijze werd ingevuld. Jij hebt een cruciale rol als research verpleegkundige gespeeld voor dit en voor alle andere gelijktijdig lopende onderzoeken. Je hebt je in korte tijd veel nieuwe taken eigen gemaakt, zoals gebruik van computers en SPSS om er slechts een paar te noemen. Geen van onze vragen was teveel en door jouw organisatorische en administratieve talenten kregen we altijd zeer snel een antwoord. Dank voor al je hulp.

Een researchafdeling functioneert niet op zichzelf. De *apotheek van het Erasmus MC* heeft dit onderzoek gesteund met hun expertise en met de productie en verzorging van de dubbelblinde medicatie. Wij zijn hiervoor veel dank verschuldigd aan *Mw. Hanff en dhr Vulto* van de apotheek (hoofd Professor Roos). *Marja Kool* van "Moleman research" heeft de gegevens zeer nauwkeurig in een database verwerkt, waarvoor mijn dank. Deze database en de data-validering zijn zeer kundig en gebruikersvriendelijk ontworpen door *Theo Broekman*, waarvoor wij hem zeer erkentelijk zijn.

Onze samenwerking met de *afdeling anesthesiologie* heeft er mede toe bijgedragen dat wij onze ECT en het wetenschappelijk onderzoek hebben kunnen verbeteren en professionaliseren. *A. Kusuma* was de eerste die de anesthesie verzorgde tijdens deze behandelingen. Later hebben wij de mogelijkheid gekregen de behandeling op onze eigen unit te kunnen uitvoeren en met name *Theo Groenland*, maar ook andere stafleden en verpleegkundigen van de afdeling anesthesiologie, hebben bijgedragen aan een vruchtbare samenwerking en aan ons gezamenlijk onderzoek. Via de afdeling anesthesie kwamen wij ook in contact met *Laraine Visser*, die met veel geduld onze engelse manuscripten heeft gecorrigeerd. Ze werden er veel leesbaarder door,

hartelijk dank.

Tini Zaanen heeft het proefschrift zijn definitieve vorm gegeven waarna het naar de drukker kon. Dank voor je hulp. *Ria van Schelven* heeft zorggedragen voor de verzending.

Jan Koolmees dank ik voor alle kilometers die wij samen hebben mogen afleggen. Deze kilometers waren voor mij een belangrijke uitlaatklep.

Mijn *medestafleden* dank ik voor hun waarneming van mijn klinische taken bij mijn afwezigheid. Tot voor kort waren we onderbemand. Desondanks hebben jullie mij in staat gesteld dit onderzoek te volooien door taken van mij, indien nodig, waar te nemen. Vooral Jan Bruijn vroeg regelmatig of hij nog iets voor mij kon doen, Jan je hebt daadwerkelijk veel voor mij gedaan en voor mij betekend.

Mijn kinderen *Stephanie en Sebastiaan* wil ik zeggen dat ik blij met ze ben. Lieve *Roos*, mijn echtgenote, mijn kameraad, dank voor al het plezier dat we gezamenlijk hebben mogen beleven. Ik hoop dat we nog vele jaren van elkaar kunnen genieten.

Curriculum vitae Walter W. van den Broek

Walter William van den Broek werd geboren op 1 April 1956 te Wassenaar. Na het behalen van het diploma Atheneum aan het Sint Maartenscollege te Voorburg studeerdee hij geneeskunde aan de Rijksuniversiteit te Leiden. Het artsexamen werd behaald op 30 augustus 1985. Na zijn artsenexamen werkte hij als agnio bij de RIAGG Noordhage te Den Haag (opleider A.C.F. Voogt).

Op 1 januari 1988 begon hij zijn basisopleiding psychiatrie in het Academisch Ziekenhuis Rotterdam-Dijkzigt te Rotterdam (opleider prof.dr. W.J. Schudel). Zijn stage sociale psychiatrie volgde hij bij de RIAGG Rotterdam-Zuid te Rotterdam (opleider A.A. de Groot). Zijn keuzejaar consultatieve en liaisonpsychiatrie in combinatie met wetenschappelijk onderzoek liep hij in het Academisch Zieknhuis Rotterdam-Dijkzigt te Rotterdam (opleider Dr. R.C. van der Mast). Hij werd ingeschreven in het specialisten register op 1 april 1992.

Sinds 1992 is hij als psychiater verbonden aan de afdeling psychiatrie van het Erasmus Medisch Centrum (hoofd: prof.dr. M.W. Hengeveld) Hij is thans medisch unithoofd van de zorglijn depressieve stoornissen.

Hij is lid van het bestuur van de sectie consultatieve en ziekenhuispsychiatrie van de Nederlandse Vereniging voor Psychiatrie, lid van de Commissie Wetenschappelijke Activiteiten van de Nederlandse Vereniging voor Psychiatrie en voorzitter van de Sponsorcommissie van de Nederlandse Vereniging voor Psychiatrie. Hij is secretaris van de Werkgroep Electroconvulsietherapie Nederland.

Publicaties W.W. van den Broek

Broek WW van den, Van Hulst AM, Klompenhouwer JL, Moleman P (1988). Lasting neurological damage with therapeutic plasma lithium levels. *Nederlands Tijdschrift voor Geneeskunde* 132:2063-2066.

Dieleman BP, Van den Broek WW, Van de Wetering BJ (1990). Abuse of anticholinergic agents. *Nederlands Tijdschrift voor Geneeskunde* 134:625-627.

Dieleman BP, Van den Broek WW, Van de Wetering BJ (1992). The suppressed medication with far-reaching consequences. *Nederlands Tijdschrift voor Geneeskunde* 136:335-336.

Aaldijk C, Van den Broek WW, Van der Mast RC (1993). De mogelijke rol van tryptofaan bij hepatische encephalopathie. *Acta Neuropsychiatrica* 4:71-75.

Naarding P, Van den Broek WW, Bruijn JA, Moleman P (1995). Addition of lithium to medication in depressive patient resistant to treatment with tricyclic antidepressive agents. *Nederlands Tijdschrift voor Geneeskunde* 139:574-577.

Leentjens AFG, Van den Broek WW, Kusuma A, Bruijn JA (1996). Facilitation of ECT by intravenous administration of theophylline. *Convulsive Therapy* 12:232-237.

Lemstra A, Leentjens AFG, Van den Broek WW (1996). Slechts tijdelijke resultaten van electroconvulsietherapie bij therapie resistente depressie; retrospectief onderzoek. *Nederlands Tijdschrift voor Geneeskunde* 140:260-264.

Bruijn JA, Moleman P, Mulder PGH, Van den Broek WW, Van Hulst AM, Van der Mast RC, Van de Wetering BJ (1996). A double-blind, fixed blood-level study comparing mirtazapine with imipramine in depressed in-patients. *Psychopharmacology* 127:231-237.

Lemstra A, Leentjens AFG, Van den Broek WW (1996). Temporary results only in electroconvulsive therapy in therapy-resistant depression; retrospective study. *Nederlands Tijdschrift voor Geneeskunde* 140:260-264.

Leentjens AFG, van den Broek, W. W., Birkenhäger, T. K., Moleman, P., & Bruijn, J. A. (1996). Effect of adjuvant drug therapy following successful electroconvulsive therapy for therapy-resistant depression is still disappointing. *Nederlands Tijdschrift voor Geneeskunde* 140:241-243.

Mast RC van der, Van den Broek WW, Fekkes D, Pepplinkhuizen L, Roest FH (1996). Delirium after cardiac surgery. The possible role of tryptophan in relation to the other neutral aminoacids. *Advances in Experimental Medical Biology* 398:93-96.

Trijsburg RW, Jelicic M, Van den Broek WW, Plekker AE, Verheij R, Passchier J (1996). Exposure and participant modelling in a case of injection phobia. *Psychotherapy Psychosomatics* 65:57-61.

Naarding P, Van den Broek WW, Koudstaal PJ (1997). Cerebrovascular lesions and depression. *Tijdschrift voor Gerontologie en Geriatrie* 28:254-259.

Broek WW van der, Van der Lely A, Neomagus G (1997). Angststoornissen. In: Hengeveld MW, H van Marwijk, J Bolk (red), *Psychiatrie in de somatische praktijk*. Houten/Diegem: Bohn Stafleu Van Loghum, pp. 44-59.

Otte W, Van den Broek WW, Birkenhäger TK, Van de Wetering BJM (1997). Het serotonine syndroom. *Tijdschrift voor Psychiatrie* 39:388-399.

Bruijn JA, Moleman P, Mulder PGH, Van den Broek WW (1998). Comparison of 2 treatment strategies for depressed inpatients: imipramine and lithium addition or mirtazapine and lithium addition. *Journal of Clinical Psychiatry* 59:657-663.

Gieteling M, Hoekstra R, Van den Broek WW, Bruijn JA (1998). A successful treatment of drug-resistant depression with electroconvulsive therapy. *Nederlands Tijdschrift voor Geneeskunde* 142:2110-2112.

Broek WW van den, Moleman P (1998). Anxiolytica en hypnotica. In: Moleman P (ed), *Praktische psychofarmacologie* (3e ed). Houten/Diegem: Bohn Stafleu Van Loghum,. pp. 1-47

Broek WW van den, Leentjens AFG, Mulder PGH, Kusuma A, Bruijn, JA (1999). Low-dose esmolol bolus reduces seizure duration during electroconvulsive therapy: a double-blind, placebo-controlled study. *British Journal of Anaesthesiology* 83:271-274.

Broek WW van den, Leentjens AFG, Verwey B (1999). *Elektroconvulsietherapie.* Houten: Bohn Stafleu en van Loghum.

Bruijn JA, Moleman P, Mulder PG, Van den Broek WW (1999). Depressed in-patients respond differently to imipramine and mirtazapine. *Pharmacopsychiatry* 32:87-92.

Mast RC van der, Van den Broek WW, Fekkes D, Pepplinkhuizen L, Habbema JD (1999). Incidence of and preoperative predictors for delirium after cardiac surgery. *Journal of Psychosomatic Research* 46:479-483.

Broek WW van den (1999). Elektroconvulsietherapie: controversen en lichtpunten. In: Den Boer JA, J Ormel, HM van Praag HGM Westenberg, H D'haenen (eds). *Handboek stemmingsstoornissen.* Maarssen: Elsevier/De Tijdstroom.

Broek WW, Huyser J, Koster AM, Stek M, Thewissen ML, Verwey B, Vleugels CMM, Van Vliet I,Wijkstra J (2000). *Richtlijn Elektroconvulsietherapie.* Amsterdam: Boom.

Mast RC van der, Van den Broek WW, Fekkes D, Pepplinkhuizen L, Habbema JD (2000). Is delirium after cardiac surgery related to plasma amino acids and physical condition? *Journal of Neuropsychiatry and Clinical Neurosciences* 12:57-63.

Bruijn JA, Moleman P, Van den Broek WW, Mulder PGH (2001). Trait anxiety and the effect of a single high dose of diazepam in unipolar depression. *Journal of Psychiatric Research* 35:331-337.

Bruijn JA, Moleman P, Mulder PGH, Van den Broek WW (2001). Treatment of mood-congruent psychotic depression with imipramine. *Journal of Affective Disorders* 66:165-174.

Hoekstra R, Van den Broek WW, Fekkes D, Bruijn JA, Mulder PGH, Pepplinkhuizen L (2001). Effect of electroconvulsive therapy on biopterin and large neutral amino acids in severe, medication-resistant depression. *Psychiatry Research* 103:115-123.

Koetsier GC, Volkers AC, Tulen JH, Passchier J, Van den Broek WW, Bruijn JA (2002). CPT performance in major depressive disorder before and after treatment with imipramine or fluvoxamine. *Journal of Psychiatry Research* 36:391-397.

Volkers AC, Tulen JH, Van den Broek WW, Bruijn JA, Passchier J, Pepplinkhuizen L (2002). 24-Hour motor activity after treatment with imipramine or fluvoxamine in major depressive disorder. *European Neuropsychopharmacology* 12:273-278.

Volkers AC, Tulen JH, Duivenvoorden HJ, Gieteling MJ, Wegewijs-De Jong M, Van den Broek WW, Passchier J, Pepplinkhuizen L (2002). Effect of personality dimensions on the diurnal pattern of motor activity. *J Pers* 70:233-247.

Felix KMLGE, Van den Broek WW, Reichart CG (2002). Elektroconvulsietherapie (ECT) bij een vijftienjarige patiente. *Tijdschrift voor Psychiatrie* 44:345-349.

Otte W, Birkenhäger TK, Van den Broek WW (2003). Fatal interaction between tranylcypromine and imipramine. *European Psychiatry* 18:264-265.

Broek WW van den, Groenland TH, Kusuma A, Mulder PGH, Bruijn JA (2003). Alfentanil has no proconvulsive effect during electroconvulsive therapy. *Canadian Journal of Anaesthesiology* 50:198-199.

Volkers AC, Tulen JH, Van den Broek WW, Bruijn JA, Passchier J, Pepplinkhuizen L (2003). Motor activity and autonomic cardiac functioning in major depressive disorder. *Journal of Affective Disorders* 76:23-30.

Kats S, Bruijn JA, Blondeau MJCE, Van den Broek WW (2003). Elektroconvulsietherapie (ECT) als dwangbehandeling. *Tijdschrift voor Psychiatrie* 45:45-49.

Birkenhäger TK, Van den Broek WW, Spijker J (2003). Farmacotherapie bij chronische depressie en dysthymie. In: Blom MBJ, J Spijker, R. van Dijck (red), *Behandelingsstrategieën bij chronische depressie en dysthymie.* Houten/Mechelen: Bohn Stafleu Van Loghum.

Broek WW van den, Birkenhäger TK, Mulder PGH, Bruijn JA, Moleman P (2004). A randomized double-blind study comparing imipramine with fluvoxamine in depressed inpatients. *Psychopharmacology, in press.*

Volkers AC, Tulen JH, Van den Broek WW, Bruijn JA, Passchier J, Pepplinkhuizen L. (2004). Effects of imipramine, fluvoxamine and depressive mood on autonomic cardiac functioning in major depressive disorder. *Pharmacopsychiatry* 37:18-25.

Broek WW van den, de Lely A, Mulder PGH, Birkenhäger TK, Bruijn JA (2004). Effect of antidepressant medication resistance on short-term response to electroconvulsive therapy (ECT). *Journal of Clinical Psychopharmacology, in press.*

Birkenhäger TK, Van den Broek WW, Mulder PGH, Bruijn JA, Moleman P (2004). A double-blind study of two-phase treatments for depressed inpatients: imipramine versus fluvoxamine, both followed by lithium addition. *American Journal of Psychiatry, in press.*

Broek WW van den, Groenland THN, Kusuma A, Mulder PGH, Bruijn JA (2004). Double-blind placebo controlled study into the effects of etomidate-alfentanil anesthesia in electroconvulsive therapy. *Journal of ECT, in press.*