# Two-year outcome of major depressive disorder in relation with dimensional subtyping.

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## Abstract

*Background:* Anxious-retarded depression is a two-dimensionally defined subcategory of depression that has been derived from the DSM-IV melancholic subcategory. This subcategory is related to increased plasma vasopressin, a high correlation between plasma vasopressin and cortisol, and a positive family history. The original melancholic subcategory is less or not related to these parameters. In the present study we explored whether anxious-retarded depression in addition has a specific outcome characteristic and is an extension of a former short report.

*Methods:* Seventy depressed patients were included to follow-up for two-years in a naturalistic treatment study. Fifty-eight patients completed the 2-year follow-up. Outcome was defined by time until full-remission, as well as by time until a Montgomery Asberg Rating Scale (MADRS) score of ≤ 10 or ≤ 15. Kaplan-Meyer survival analyses and Cox regression analyses were used to compare outcome in anxious-retarded depression and the group of all other depressed patients. Similar analyses were performed to compare melancholic and non-melancholic patients.

*Results:* Anxious-retarded depression had a poor outcome. Melancholic patients did not differ from non-melancholic patients in any outcome measure.

*Limitations:* The number of patients was small and too small for the analysis of the confounding effect of the melancholic subcategory.

*Conclusion:* The validity of the anxious-retarded subcategory of depression that is characterized by vasopressinergic overactivation of the HPA-axis and a positive family history of depression is further supported by a poor outcome compared to non-anxious-retarded depressed patients.

*Key words:* Melancholia, dimensions, anxiety, psychomotor retardation, anxious-retarded and outcome.

## 1. Introduction

An anxious-retarded subcategory of depression has been derived from the melancholic subtype according to DSM-IV by using a global multidimensional structure of psychopathology (de Winter et al., 2004. This anxious-retarded subcategory has been found to have a higher correlation between plasma AVP and cortisol and a higher level of plasma AVP than all other depressed patients (de Winter et al., 2003). Moreover, the anxious-retarded subcategory appeared to be related to a positive family history of depression (de Winter et al., 2004). The melancholic subcategory was less or not related to these parameters.

In this paper we describe a next step of the validation programme proposed by Robins and Guze (Robins and Guze, 1970), by investigating the long-term outcome of the anxious-retarded subcategory in comparison with all other depressed patients. Since anxious-retarded depression has been derived from the melancholic subcategory, we in addition investigated the outcome in melancholic patients compared with non-melancholic patients.

Many factors have been found to be related to outcome of depression: The melancholic subcategory (Tuma, 2000), endogenous depression (O'Leary, 1996), symptom severity and duration of illness (Keller et al., 1992), retardation (van Londen et al., 1998), anxiety (Coryell et al., 1992), neuroticism (Scott et al., 1992), a positive family history of depression (Kendler et al., 1997), female gender (Sargeant et al., 1990), older age and lower education (Ronalds et al., 1997), comorbid psychiatric and somatic co-morbidity (Keitner et al., 1991) and family history of mental disorder (Duggan et al., 1998). In the present study we investigated the role of these factors except for the last two, as covariates related to the outcome of anxious-retarded and melancholic depression. ). A former short study was published in (de Winter et al., 2005) and this is an extension of this short report.

Outcome was primarily defined as the time to full-remission according to DSM-IV, corresponding with the criteria formulated by Frank and others (≤ 2 DSM-IV symptoms) (Frank et al., 1991). For comparability with other investigations we used two other outcome measures derived from the Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979, Keller, 2003): The time needed to reach a score ≤ 10 as a criterion for remission of major depressive disorder (MDD), or a score ≤ 15 as a criterion for full treatment response.

## 2. Methods

### *2.1. Patients*

The depressed patients who participated in this study were recruited in the inpatient and outpatient clinic of the general psychiatric hospital Endegeest from December 1995 to June 1998. The patients were a subsample of the sample previously used for crossectional analysis (de Winter et al., 2003; de Winter et al., 2004). A psychiatrist at the inpatient or outpatient clinic made primarily the diagnosis of major depression (DSM-IV). If R.F.P. de W. confirmed this diagnosis, the patient was asked to participate in the study. Other inclusion criteria were a MADRS score of 21 or higher, age between 18 and 65 years and if the first episode was before the age of 60 years. Patients with organic disorder and patients with bipolar, PTSD, schizoaffective, schizophrenic or other primary psychotic disorder were excluded. Depressed patients with a panic disorder were not included, since they participated in a different research project. Other exclusion criteria were a history of alcohol or drug abuse or dependence. Patients were also excluded if they had pregnancy, clinical evidence of endocrine disease, dementia or a medical illness that could influence plasma levels of vasopressin and cortisol. All patients underwent routine blood analysis.

The Medical Ethics Committee of the Leiden University Medical Center approved the research protocol, and written informed consent was obtained of each patient after complete description of the study.

*2.2 Assessment*

The DSM-IV subcategories of depression were assessed by using semi-standardized interviews for these subtypes. The anxious-retarded subcategory was defined as the combination of high anxiety (above median scores for both autonomic dysregulation (≥11)) and high retardation (motivational inhibition (≥8)) (de Winter et al., 2003) on the Comprehensive Psychopathological Rating Scale (CPRS) (Åsberg et al., 1978; Goekoop et al., 1991). These two dimensions are part of six basic dimensions previously found in a heterogeneous patient sample using the CPRS (Goekoop et al., 1992).

A slightly modified version of the Family History of the RDC interview by Andreasen assessed familial depression. (Andreasen et al., 1986; de Winter et al., 2004). Neuroticism was measured by the Eysenck Personality Questionnaire (Eysenck and Eysenck, 1975). Education level was classified in six categories (level 1 = no or low education until level 6 = University or postgraduate).

*2.3. Treatment*

All patients were treated according to the same therapeutic protocol comprising pharmacotherapy (see below) and a standardized treatment with cognitive behavioural therapy, starting with behavioural activation. If necessary, relational therapy, daytime treatment or clinical treatment was added. If a patient was already taking an antidepressant, this treatment was continued and increased to a maximal therapeutic dose. If the

antidepressant drug at entrance of this study had to be changed because of lack of treatment effect at the start of this study, drug withdrawal was performed after the first assessment of the study.

The pharmacotherapeutic programme comprised: 1. venlafaxine with a maximum of 225 mg/day for outpatients and 275 mg/day for inpatients. 2. Patients unresponsive to venlafaxine after 6 weeks at maximum dose were treated with amitriptylin, 200 mg/day for outpatients and 300 mg/day for inpatients. 3. If patients failed to respond after six weeks of maximum dose amitryptylin, lithium carbonate was added. 4. When patients still did not show clinical improvement tranylcypromine was substituted for amitriptylin. 5. When patients after 6 weeks of maximally 80 mg tranylcypromine treatment did not improve, a course of electroconvulsive therapy was recommended.

*2.4. Follow-up and outcome measures*

Psychopathology was assessed with the CPRS at the beginning of the treatment (t1), six weeks later (t2) and than after 3, 6, 12 18 and 24 months (t3 – t7)),

The general intensity of the depressive disorder was rated each time with a subscale of the CPRS, the Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979). A MADRS score of less than or equal to 10 was used as criterion for remission, and a MADRS score ≤ 15 as criterion for treatment response (Keller, 2003).

Full remission was defined by a maximum of 2 symptoms for major depression according DSM-IV during at least the last 2 weeks. Partial remission was defined by a minimum of 3 and a maximum of 4 symptoms of major depression according DSM-IV during at least the last 2 weeks (Frank et al., 1991). To this end all CPRS items were rated from 0 – 6, covering the two weeks preceding the assessment.

DSM-IV criteria were derived from the corresponding CPRS items. For this purpose the scores on the individual items were dichotomised: Scores ≥ 3 were taken as representing the DSM-IV severity criterion of a symptom being more present than absent. Increased appetite and weight were rated separately. The absence of a DSM-IV symptom was defined by the intensity of a CPRS item score ≤ 2.

*2.5. Data analysis*

The Mann-Whitney U test, *t* test and $\chi^2$ were used for differences between subgroups of patients for demographic and clinical data (age, gender, age-onset, previous episodes of MDD, duration of illness, out- or inpatient status, educational level, family history for MDD, neuroticism, married status, initial MADRS score and DSM-IV or two-dimensionally subcategorisation).

Kaplan-Meier curves were made and Cox regression analyses (forward stepwise) were used to test whether the subcategories (anxious-retarded-depression, high anxiety depression, high retardation depression and melancholic depression) differed from the patient control group in outcome defined by the three outcome criteria.

Cox regression analysis was also used for covariate analysis. Covariates were age, gender, family history, severity of symptoms (MADRS score), duration of illness, periods of illness, neuroticism and education.

The Statistical Package for Social Sciences version (SPSS 9.0 INC, Chicago) was used for statistical analysis.

## 3. Results

*3.1. Clinical characteristics*

From the 70 patients included for the two-year follow-up, 47 were female and 23 male, 48 patients had a stable relation (31 married status), and 28 were inpatients. Age ranged between 20 and 64 years, (mean 38.6, standard deviation (SD) ± 11.2 years). For 26 patients it was the first episode of major depression, for 25 patients the second or third time and for 19 patients it was at least the fourth time. The average duration of symptoms for major depression before the initial measurement was 6.7 months (SD 6.9 months, 1-42 months). The mean age of onset of the first affective disorder is 29.3 years (SD 12.6 years). Two patients committed suicide during follow-up between t1 and t2, and t2 and t3, respectively. One of these patients fulfilled criteria for melancholic, psychotic and anxious-retarded depression, the other for melancholic depression only.

One patient became pregnant during follow-up, six patients refused further participation during follow-up (4 female and 2 male) and 3 patients (2 male and 1 female) were lost due to moving to another location. This resulted in 58 patients available in the two-year follow-up.

At initial measurement from the 70 patients, 24 patients had anxious-retarded depression, 33 patients fulfilled criteria for the melancholic subcategory (DSM-IV), ten patients had depression with psychotic features, and fourteen patients fulfilled criteria for atypical depression. From the 33 patients with melancholic features, 20 had anxious-retarded depression ($\chi^2 = 19.2$, df = 1 and $P < 0.0001$) and 8 patients had psychotic features ($\chi^2 = 5.06$, df = 1 and $P= 0.025$). None of the melancholic patients had atypical depression ($\chi^2 = 15.61$, df = 1 and $P= 0.0001$). From the 24 anxious-retarded patients 20 patients fulfilled criteria for the melancholic subcategory ($\chi^2 = 19.2$, df = 1 and $P < 0.0001$), six had psychotic features ($\chi^2 =$

3.42, df = 1 and P = 0.064), and none of these patients fulfilled criteria for atypical depression ($\chi^2$ = 9.1, df = 1 and P= 0.003).

There were no clinical or demographic differences between patients lost in the follow-up and those remaining in the follow-up ($\chi^2$, *t* test or Mann-Whitney U, P> 0.05).

*3.2. Clinical or demographic differences between the different subcategories*

Anxious-retarded depression showed more often a positive family history for MDD than all other patients ($\chi^2$ = 6.32, df = 1 and p = 0.012), the patients of the melancholic subcategory were less often married than the non-melancholic patients ($\chi^2$ = 4.95, df = 1 and p = 0.026) There were further no clinical or demographic differences between the different subcategories and their patient control group ($\chi^2$, *t* test or Mann-Whitney U, P> 0.05).

*3.3. Outcome according DSM-IV criteria.*

Figures 1 show rates of full remission and non-remission in the whole group of depressed patients and anxious-retarded-depression during two years of follow-up.

< figure 1 about here >

Table 1 shows percentages of patients still fullfilling criteria for MDD criteria, partial remission and full remission in all patients, patients with the melancholic subcategory and patients with anxious-retarded depression.

< table 1 about here >

*Survival analysis of the anxious-retarded subcategory*

The patients with anxious-retarded depression did differ significantly from all other patients in duration of time to full remission (Wald = 7.85, df = 1 and p = 0.005) (see figure 3). Analysis of covariate effects did not result in altered Wald and P values.

The dichotomised scores for initial high or low anxiety and high or low retardation apart did not significantly relate to duration of time to full remission (for anxiety; Wald = 1.16, df = 1 and p = 0.204, and for retardation; Wald = 2.08, df = 1 and p = 0.149).

< figure 2 about here >

*Survival analysis of the melancholic subcategory*

The patients fulfilling criteria for the melancholic subcategory did just not differ significantly from the patients with non-melancholic depression in duration of time to full remission (Wald = 3.21, df = 1 and p = 0.073). Analysis of covariate effects did not result in altered Wald and P values.

*3.4. Outcome in terms of MADRS criteria*

The mean values and standard deviations (SD) of the MADRS for the whole group, the melancholic subcategory and anxious-retarded-depression are presented in table 2.

< table 2 about here >

*Survival analysis of the anxious-retarded subcategory*

The patients with anxious-retarded depression did differ significantly from the other patients with depression in duration of time reaching the MADRS score ≤ 15 during follow-up (Wald

= 4.66, df = 1 and p = 0.030) and a MADRS score ≤ 10 (Wald = 4.17, df = 1 and p = 0.041). After covariate analysis as described before (of course without MADRS score), the statistical significance remained the same for both MADRS criteria.

The initial dichotomised scores for high or low anxiety and high or low retardation apart did not significantly relate to duration of time reaching the MADRS score ≤ 15 during follow-up (for anxiety; Wald = 2.64, df = 1 and p = 0.104, and for retardation; Wald = 1.29, df = 1 and p = 0.256) and a MADRS score ≤ 10 during follow-up (for anxiety; Wald = 1.62 df = 1 and p = 0.204, and for retardation; Wald = 2.08, df = 1 and p = 0.149).

*Survival analysis of the melancholic subcategory*

The patients fulfilling criteria for the melancholic subcategory did not differ significantly from the patients with non-melancholic depression in duration of time until the MADRS ≤ 15 (Wald = 2.89, df = 1 and p = 0.09) and a MADRS ≤ 10 (Wald = 0.93, df = 1 and p = 0.334). Covariate analysis (of course without MADRS score) did not result in altered Wald and P values.

## 4. Discussion

In the present study 57% of all patients showed full remission after one year, 20% showed partial remission, leaving 23% of all patients unremitted. The full remission rate increased after two-years to 71%, while partial remission decreased to 14%, leaving 16 % of all patients unremitted. These remission rates for MDD are comparable with previous findings. (Keller et al., 1992; Ramana et al., 1995; van Londen et al., 1998, Pintor et al., 2003).

The two-dimensionally constructed anxious-retarded subcategory had a poor outcome in terms of a longer time to full remission during two years of follow-up, compared to all other depressed patients. The anxious-retarded subcategory also needed a longer time to reach the MADRS score of ≤15 or ≤10 during two years of follow-up, when compared to all other patients. The melancholic subcategory, from which the anxious-retarded subcategory was derived, did not differ from the non-melancholic patients in these respects. The combination of high anxiety and high retardation was required for this prediction, since the dichotomised scores for anxiety and retardation separately were not significantly related to outcome.

The poor outcome of the anxious-retarded subcategory in this study seemed not homogeneously distributed. After two years these patients were generally either fully remitted or still depressed. Only one patient was partially remitted (5%). In contrast the melancholic subcategory showed similar remission rates as in the whole group. The partial remission rates of these groups were 14%. Although the number of patients involved in this study is relatively small, the data suggest a potential differentiation of outcome specific for the anxious-retarded subcategory. The number of patients was also too small for the analysis of the confounding effect of the melancholic subcategory.

The DSM-IV definitions for partial remission and full remission used in this study were defined for a period of 2 weeks, corresponding with the minimum criteria proposed by

Frank et al (Frank et al., 1991). Recovery as they did define it could not be assessed, since that recovery was defined by a period of 8 weeks or longer. Therefore we were not able to differentiate between remission and recovery. The definition for remission in the present study may better be labeled as “onset of full remission and onset of partial remission” as defined by O'Leary et al (O’Leary et al., 2000) after the end of our study.

Previous studies showed an effect of several clinical and demographic variables on duration of depression. We analysed the following "potential covariates": symptom severity and duration of illness (Keller et al., 1992), retardation (van Londen et al., 1998), anxiety psychiatric and somatic co-morbidity (Keitner et al., 1991; Coryell et al., 1992), family history for a mental disorder (Duggan et al., 1998), a positive family history of depression (Kendler et al., 1997), female gender (Sargeant et al., 1990), neuroticism (Scott et al., 1992), older age and lower education (Ronalds et al., 1997). Somatic comorbidity was not analysed because all patients were generally in good health. In the present study none of the other "covariates" showed an effect on outcome.

Anxious-retarded depression is based on a combination of high ratings on two dimensions: motivational inhibition (retardation) and autonomic dysregulation (anxiety). Up to now, the combination of high anxiety and retardation has not been used to assess outcome. On the other hand anxiety and retardation have separately been used to analyse dependence of poor outcome in depression: In one study depressed patients with higher ratings for anxiety took longer to recover (Clayton et al., 1991). It is unclear whether these anxiety symptoms are comparable with the items for the dimension autonomic dysregulation we used. In terms of categorical disease concepts anxious depression may be conceived as co-morbidity of an anxiety disorder with depression. The present findings may therefore be seen as corresponding with and a potential amelioration of the finding that this co-morbidity is associated with poor outcome (Bakish, 1999; Clayton et al., 1991; Coryell et al., 1992).

Retardation has been associated with a better response on antidepressants and ECT, and therefore could be related to good outcome (Sobin & Sackheim, 1997). In contrast to this expectation, a high CORE score, indicating the intensity of psychomotor retardation, has been found to predict less remission in melancholic patients after one year (Parker et al., 1992). Face validity comparison suggests that 3 of the 5 items of the CPRS dimension "motivational inhibition" overlap with items of the CORE. Psychomotor retardation measured by the Sâlpetrière Retardation Rating Scale (SRRS) has also been found to predict a longer time to partial remission (van Londen et al., 1998). In the present study, however, only the combination of anxiety and retardation was related to outcome. We therefore conclude that combined anxiety and retardation may have higher predictive value for outcome than either dimension apart.

This study can be seen as one of the steps for the validation of the anxious-retarded subcategory of depression that we previously derived from the melancholic subcategory. This anxious-retarded subcategory showed a significant correlation between plasma AVP and cortisol, and was also associated with a higher level of plasma AVP (de Winter et al., 2003). The anxious-retarded subcategory also appeared to be related to a positive family history for depression (de Winter et al., 2004). The melancholic subcategory did not show these relations. We now added to these relations the characterisation of a poor outcome. Due to these relations the two-dimensionally defined anxious-retarded subcategory may have a higher external validity than the melancholic subcategory from which it is derived.

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Figure 1: remission and MDD rates for anxious-retarded and for all patients during follow-up

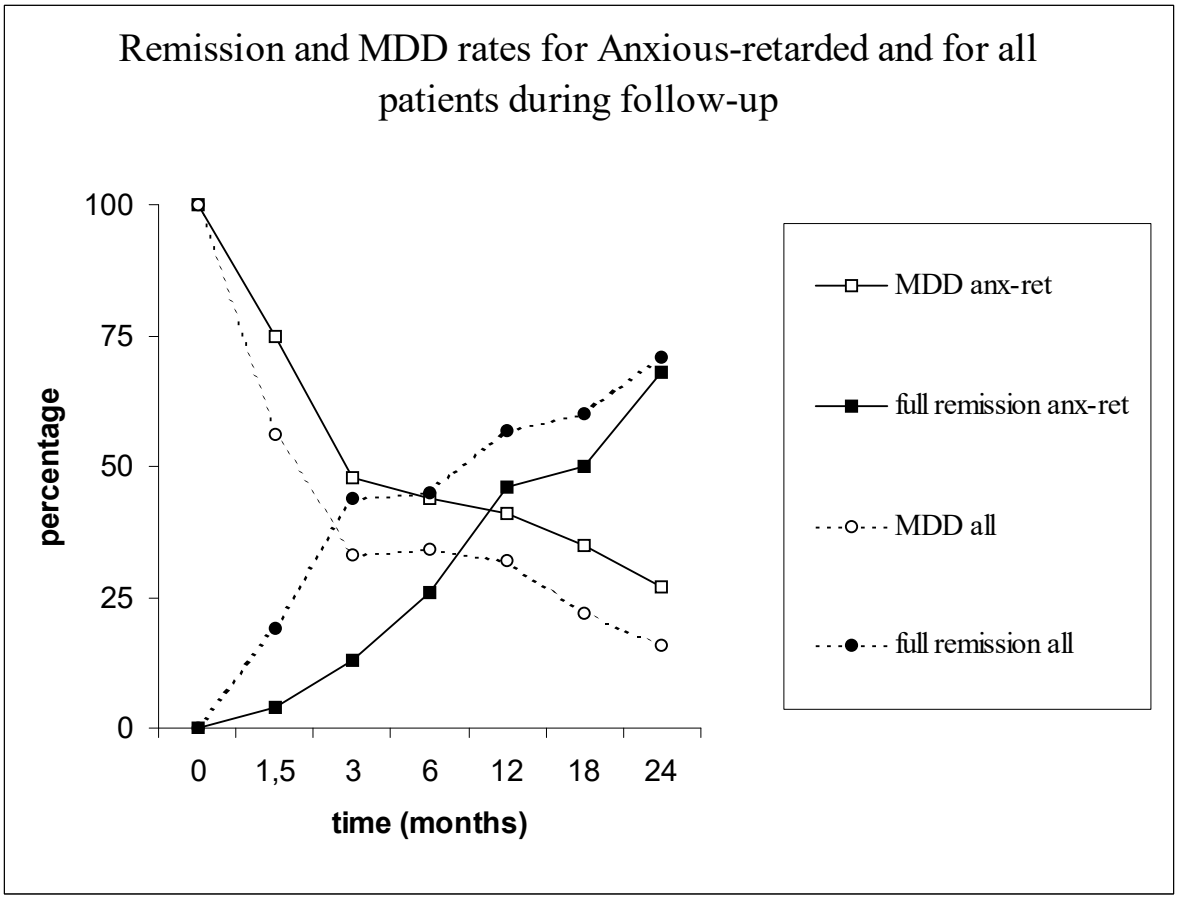

Figure 2: Kaplan Meier curve for the anxious-retarded subcategory and full remission of MDD

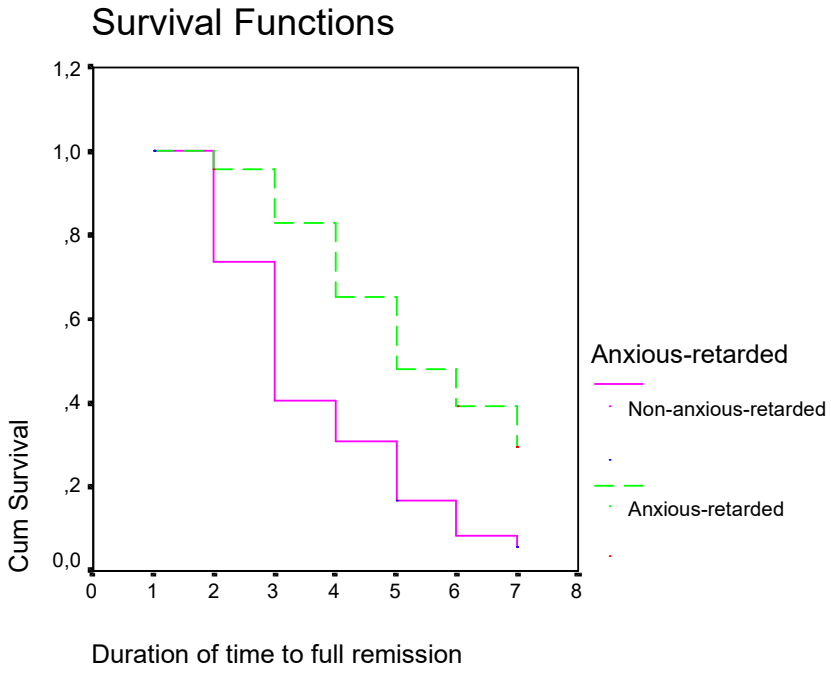

Table 1 Percentages (rounded) of patients fullfilling criteria for MDD criteria, partial remission and full remission in all patients, patients with the melancholic subcategory and patients with anxious-retarded depression.

| **MDD and subcategory** | 6 weeks percentage (n) | 3 months % (n) | 6 months % (n) | 1 year % (n) | 18 mnths % (n) | 2 years % (n) |
|---|---|---|---|---|---|---|
| All patients: | | | | | | |
| MDD | 56% (37) | 33% (21) | 34% (22) | 23% (14) | 22 % (12) | 16 % (9) |
| Partial remission | 25% (16) | 23% (15) | 21% (14) | 20% (12) | 18% (12) | 14% (8) |
| Full remission | 19% (12) | 44% (28) | 45% (29) | 57% (35) | 60% (33) | 71% (41) |
| Melancholic: | | | | | | |
| MDD | 69% (22) | 40% (12) | 39% (12) | 27% (8) | 19% (5) | 18% (5) |
| Partial remission | 25% (8) | 33% (10) | 32% (10) | 27% (8) | 15% (4) | 14% (4) |
| Full remission | 6% (2) | 27% (8) | 29% (9) | 47% (14) | 65% (17) | 68% (19) |
| Anxious-retarded: | | | | | | |
| MDD | 75% (18) | 48% (11) | 44% (10) | 41% (9) | 35% (7) | 27% (6) |
| Partial remission | 21% (5) | 39% (9) | 30% (7) | 14% (3) | 15% (3) | 5% (1) |
| Full remission | 4% (1) | 13% (3) | 26% (6) | 46% (10) | 50% (10) | 68% (15) |

Table 2 Ratings of the MADRS score (and standard deviation between brackets) during follow-up for differently defined subcategories of depression.

| **(Sub)category of depression** | Start<br>score (SD) | 6 weeks<br>score (SD) | 3 months<br>score (SD) | 6 months<br>score (SD) | 1 year<br>score (SD) | 18 months<br>score (SD) | 2 years<br>score (SD) |
|---|---|---|---|---|---|---|---|
| All patients | 30.1 (*6.2)* | 23.9 (*8.1)* | 20.5 (*9.3)* | 20.3 (*9.5)* | 16.4 (*9.2)* | 16.3 (*9.3)* | 13.6 (*8.7)* |
| Melancholic | 34.2 *(6.1)* | 26.1 *(7.4)* | 23.6 *(8.0)* | 22.3 *(9.2)* | 18.3 *(9.5)* | 16.0 *(9.3)* | 15.1 *(9.6)* |
| Non-melancholic | 26.4 *(3.4)* | 21.8 (*8.3)* | 17.8 *(7.9)* | 18.5 *(9.5)* | 14.5 *(8.6)* | 16.5 *(9.5)* | 12.2 *(7.7)* |
| Anxious-retarded | 35.9 *(5.4)* | 28.0 *(5.5)* | 25.7 *(6.3)* | 23.3 *(8.8)* | 19.7 *(9.3)* | 19.4 *(9.6)* | 16.7 *(10.0)* |
| Non-anxious-retarded | 27.0 (*4.1)* | 21.4 *(8.5)* | 17.6 *(9.5)* | 18.7 *(9.5)* | 14.5 (*8.7)* | 14.5 (*8.8)* | 11.8 *(7.4)* |

**Pharmacotherapy**

From the 70 patients at T1, 61 patients used at least one psychotropic drug: 41 patients used an antidepressant, 37 patients used a benzodiazepine and 9 patients a neuroleptic. From the 65 patients at t2, 61 patients used at least one psychotropic drug: 50 patients used an antidepressant, 35 patients used a benzodiazepine and 6 patients a neuroleptic. From the 64 patients at t3, 56 patients used at least one psychotropic drug: 49 patients used an antidepressant, 36 patients used a benzodiazepine and 7 patients a neuroleptic.

From the 64 patients at t4, 56 patients used at least one psychotropic drug: 50 patients used an antidepressant, 38 patients used a benzodiazepine and 6 patients a neuroleptic.

From the 61 patients at t5, 45 patients used at least one psychotropic drug: 41 patients used an antidepressant, 23 patients used a benzodiazepine and 6 patients a neuroleptic.

From the 55 patients at t6, 39 patients used at least one psychotropic drug: 34 patients used an antidepressant, 20 patients used a benzodiazepine and 4 patients a neuroleptic.

From the 58 patients at t7, 33 patients used at least one psychotropic drug: 33 patients used an antidepressant, 18 patients used a benzodiazepine and 6 patients a neuroleptic.

**Differences in subcategories for pharmacotherapy**

Melancholic patients used more often benzodiazepines than the non-melancholic subcategory at time point 1 (66% versus 41%, $\chi^2 = 4.77$, df = 1 and P = 0.029), time point 2 (68% versus 42 %, $\chi^2 = 4.313$. df = 1 and P = 0.042) and at time point 3 (70% versus 44%, $\chi^2 = 4.338$, df = 1 and P = 0.037). Patients with the melancholic subcategory used also more often neuroleptics at time point 1 than the non-melancholic subcategory (21% versus 5 %, $\chi^2 = 3.89$, df = 1 and P= 0.049). After correction for multiple assessments these relations lost statistical significance.

No difference was found between the anxious-retarded subcategory and all other patients for the use of benzodiazepines, antidepressant or antipsychotic drugs.