



Psychomotor Retardation and the prognosis of antidepressant treatment in patients with unipolar Psychotic Depression

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ABSTRACT

Background: Psychomotor Retardation is a key symptom of Major Depressive Disorder. According to the literature its presence may affect the prognosis of treatment. Aim of the present study is to investigate the prognostic role of Psychomotor Retardation in patients with unipolar Psychotic Depression who are under antidepressant treatment.

Methods: The Salpatriere Retardation Rating Scale was administered at baseline and after 6 weeks to 122 patients with unipolar Psychotic Depression who were randomly allocated to treatment with imipramine, venlafaxine or venlafaxine plus quetiapine. We studied the effects of Psychomotor Retardation on both depression and psychosis related outcome measures.

Results: 73% of the patients had Psychomotor Retardation at baseline against 35% after six weeks of treatment. The presence of Psychomotor Retardation predicted lower depression remission rates in addition to a higher persistence of delusions. After six weeks of treatment, venlafaxine was associated with higher levels of Psychomotor Retardation compared to imipramine and venlafaxine plus quetiapine.

Conclusions: Our data confirm that Psychomotor Retardation is a severity marker of unipolar Psychotic Depression. It is highly prevalent and predicts lower effectivity of antidepressant psychopharmacological treatment.

1. Introduction

Psychomotor Retardation is a key symptom of Major Depressive Disorder (MDD) (American Psychiatric Association, 2013). It is characterized by slowness in both cognitive and motor processing and can be observed in speech, thinking and body movements (Schrijvers et al., 2008). In patients with unipolar depression prevalences of 60–70% have been established (Novick et al., 2005).

Psychomotor Retardation is a severity marker of depression. It is associated with several characteristics indicating a severe course of depression including an early age of onset, a longer duration of illness, a higher number of depressive episodes and increased rates of suicide attempts (Calugi et al., 2011). In addition, Psychomotor Retardation is the primary symptom delineating the more severe melancholic subtype from non-melancholic depression (Parker, 2000; Parker and McCraw,

2017).

Possibly related to its association with depression severity, literature suggests that the presence of Psychomotor Retardation could inform treatment choice: patients with Psychomotor Retardation responded poorly to Selective Serotonin Reuptake Inhibitors (SSRIs) (Schrijvers et al., 2008; Ulbricht et al., 2018). More positive results were found for Tricyclic Antidepressants (TCAs), other dual acting antidepressants and combinations of serotonergic and noradrenergic agents (Sobin and Sackeim, 1997; Schrijvers et al., 2008). Psychomotor Retardation predicted a higher treatment response in patients selected for Electroconvulsive Therapy (Hickie et al., 1996; van Diermen et al., 2019; Heijnen et al., 2019).

Although Psychomotor Retardation is very common in Psychotic Depression, with a reported prevalence of up to 75% (Parker et al., 1991), little research has been conducted to its role in the

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pharmacological treatment of patients with Psychotic Depression. Additional research is important to conclude if Psychomotor Retardation influences the outcome of pharmacological treatment, as is the case in non-Psychotic Depression. The main aim of this study is to evaluate the role of Psychomotor Retardation as a predictor of treatment response, taking different outcome measures into account. Based on the associations with severity in patients with non-psychotic MDD (Calugi et al., 2011), we hypothesize that the presence of Psychomotor Retardation predicts a lower response to pharmacological treatment.

2. Methods

We used data from a multicentre, double-blind randomized controlled trial comparing the efficacy of imipramine (Tricyclic Antidepressant), venlafaxine (Serotonin-Noradrenaline Reuptake Inhibitor) and venlafaxine plus quetiapine (2nd generation antipsychotic agent) in patients with unipolar Psychotic Depression. The complete description of the study can be found elsewhere (Wijkstra et al., 2010). Here, we present a summary of the methods.

2.1. Patients

Hospitalized patients aged 18–65 years were included if they met DSM-IV-TR criteria (American Psychiatric Association, 2000) for unipolar major depressive episode with psychotic features and a score ≥ 18 on the Hamilton Rating Scale for Depression (HAM-D; 17 item version; Hamilton, 1960) both at the screening visit and at the day prior to start of medication. Exclusion criteria were: an acute indication for electroconvulsive therapy (ECT); mental retardation; alcohol or substance abuse or dependence within 3 months of enrolment; any serious somatic illness; somatic medication affecting mood; contraindications for study medication; adequate previous treatment of the current episode with imipramine (≥ 4 weeks with adequate plasma levels (200–300 $\mu\text{g/l}$) or venlafaxine (≥ 4 weeks ≥ 300 mg/day).

2.2. Study design

The study was approved by the ethical review board of the University Medical Centre Utrecht, and by the local review boards of the participating centres, and performed according to the rules of Good Clinical Practice. All patients, or their legal relatives in case of incapacity, gave written informed consent prior to enrolment.

The diagnosis of unipolar Psychotic Depression was confirmed using the Structured Clinical Interview for DSM-IV Axis I disorders (First, 1999). Baseline assessments also included a psychiatric history, a medical history and a physical examination including vital signs and routine laboratory assessments. There were weekly assessments of depressive symptoms (HAM-D) and positive psychotic symptoms (hallucinations and/or delusions). All assessments were performed by trained physicians.

All patients were drug free for at least 4 days before the start of treatment. After inclusion, they were randomized to 7 weeks double-blind treatment with imipramine, venlafaxine, or venlafaxine plus quetiapine, while stratifying for centre. Study drugs were dosed to reach an adequate plasma level (200–300 $\mu\text{g/l}$ for imipramine) or the maximum dose (375 mg/day for venlafaxine and 600 mg/day for quetiapine). As concomitant psychotropic medication, only benzodiazepines at a maximum of 3 mg lorazepam equivalent per day were allowed.

2.3. Psychomotor retardation

Psychomotor Retardation was measured at baseline and after 6 weeks using the Salpetriere Retardation Rating Scale (SRRS; Dantchev and Widlocher, 1998). The SRRS is a clinician rated instrument, consisting of 14 individual items plus a final appreciation. Items are scored

on a five point likert scale ranging from 0 (normal) to 4 (severe disturbance) and refer to motor function, speech and objective and subjective mental activity (Dantchev and Widlocher, 1998). For the Dutch version good internal consistency was confirmed. Interrater reliability was sufficient to good. Convergent validity was indicated by a high association between the SRRS score and the retardation items of the Comprehensive Psychopathological Rating Scale (de Weme et al., 1996).

Measures of Psychomotor Retardation:

- The SRRS-6 score, is the sum score of the first six SRRS items. This subscale includes only objective (assessor observed) items, while the complete SRRS scale also relies on the subjective experiences of patients which might be biased by depression (Brebion et al., 1997; Lampe et al., 2001; Smith et al., 1994).
- Clinical Psychomotor Retardation, defined as a total SRRS score above the cut-off of 20 points (Widlocher, 1983).
- HAM-D retardation (HAM-D item 8; score 0 or 1 coded as absent; score ≥ 2 coded as present). This dichotomized score reflects presence or absence of psychomotor retardation, not severity. In the present study the HAM-D retardation score was only used for cross-validation of the SRRS based scores.

2.4. Outcome measures

Outcome of pharmacological treatment was measured after 7 weeks. The primary outcome measure is response, defined as a HAM-D score of ≤ 14 and a $\geq 50\%$ decrease from baseline. The maximum score of 14 in this definition was also applied in the primary study (Wijkstra et al., 2010) and was chosen to preclude moderate to severe depression in patients who reached response. Secondary outcome measures were: a) treatment remission defined as HAM-D ≤ 7 ; b) the presence of hallucinations and c) the presence of delusions. Assessments of hallucinations and delusions were based on psychiatric interview and clinical observations (scored 1 if present and 0 if absent).

Administration of HAM-D, SRRS and other measures was discussed at regular meetings with the researchers from all participating sites. Inter-rater reliability as indicated by the intraclass correlation coefficient and based on three patients and eight raters was 0.93 (95% CI: 0.74; 1.00) for the HAM-D.

2.5. Statistical analysis

Univariate associations were expressed as Pearson's correlation coefficients. For testing of changes in categorical and dimensional measures we used chi-square tests and paired t-tests respectively.

Logistic regression analysis was carried out to study the prognostic effects of Psychomotor Retardation on the outcome of psychopharmacological treatment. Here we used the intention-to-treat (ITT) principle. According to this principle all randomized patients are included for statistical analysis regardless of whether they completed follow-up. In case of dropout we used the last observation carried forward method.

The primary analyses were adjusted for the most important potential confounders: age, gender, baseline HAM-D score without retardation item, recent antipsychotic medication and drug type. Subsequently these analyses were adjusted for the number of previous depressive episodes and duration of the current episode. In supplementary analyses we investigated the contribution of the interactions of treatment strategy and Psychomotor Retardation by adding the three products of treatment group by baseline SRRS-6 score.

Finally, in a multiple regression analysis we compared the effects of the treatment conditions on the outcome of psychomotor retardation (SRRS-6-score) adjusting for the baseline SRRS-6 score, baseline HAM-D score without retardation item age and gender.

All analyses were conducted with SPSS 25.0 for Windows (SPSS IBM CORP, 2017). The significance level was set at $p < 0.05$ (two sided).

3. Results

Table 1 presents the baseline characteristics of the study sample. A total of 122 patients was included. After randomisation 39 patients (32.0%) were treated with venlafaxine, 42 (34.4%) with imipramine and 41 (33.6%) with venlafaxine plus quetiapine. Treatment groups were comparable for baseline clinical and demographic characteristics.

Eight subjects used antipsychotic medication before the one-week washout period. The association between antipsychotic use and baseline SRRS-6 score was insignificant ($r = 0.006$ NS).

Correlations between the baseline measures of Psychomotor Retardation were highly significant: SRRS-6 by SRRS total score $r = 0.92$ $p < 0.001$; SRRS-6 by HAM-D retardation item $r = 0.77$ $p < 0.001$. The SRRS-6 score had a positive significant association with the number of previous depressive episodes ($r = 0.19$ $p = 0.03$) and the baseline total HAM-D score ($r = 0.28$ $p = 0.002$). When the HAM-D retardation item was excluded from the total baseline HAM-D score, the association was no longer significant ($r = 0.13$ NS). Correlations between the SRRS-6 score and other baseline clinical characteristics (duration current depressive episode, presence of delusions and hallucinations) and demographic variables (age and gender) were low and insignificant.

During treatment a total of 76.2% of the patients ($n = 93$) used benzodiazepines (imipramine group 32/42 (76.2%); venlafaxine group 30/39 (76.9%); venlafaxine plus quetiapine group 31/41 (75.6%); $\chi^2 = 0.02$ NS). There were no significant associations between benzodiazepine use and SRRS-6 scores at baseline and after 6 weeks of treatment (baseline $r = -0.12$ NS; after 6 weeks $n = 103$ $r = -0.13$ NS).

Table 2 presents the measures of Psychomotor Retardation at baseline and after 6 weeks of treatment. Results are presented for categorical measures (Clinical Psychomotor Retardation defined as a SRRS score above 20; HAM-D retardation as an item score above 1) and for dimensional measures (SRRS total score and SRRS-6 score). In 73% of the patients there was evidence of Clinical Psychomotor Retardation at baseline which decreased to 35% after 6 weeks. Three patients who did not fulfil criteria at baseline developed Clinical Psychomotor Retardation during treatment. The decrease in retardation scores during treatment was comparable for all Psychomotor Retardation measures (range 31.1–40.2%). Taking only the results of patients with complete SRRS scores after six weeks into account, the change in SRRS-6 scores during treatment was significantly associated with the change in HAM-D scores ($r = 0.28$ $p < 0.006$ $n = 103$). After 6 weeks of treatment the correlation between the SRRS-6 score and the HAM-D score was 0.58 ($p < 0.001$ $n = 103$).

Table 3 presents the HAM-D scores and the rates of positive psychotic symptoms at baseline and after 7 weeks of treatment.

Hallucinations at baseline were present in a minority of the patients while almost all patients had delusions. In about half of the patients hallucinations had remitted after 7 weeks. Delusions remitted in about two thirds of the patients.

Table 4 presents the associations between baseline Psychomotor

Table 1
Baseline demographic and clinical characteristics.

	Total group	Venlafaxine	Imipramine	Venlafaxine plus Quetiapine	Differences between treatment groups ^a		
	N = 122	N = 39	N = 42	N = 41	Statistics	df	p-value
Age in years (M, SD)	51.0 (10.9)	50.0 (12.0)	51.9 (9.6)	50.9 (11.1)	F = 0.3	2	0.73
Female gender (N,%)	62 (50.8%)	17 (43.6%)	23 (54.8%)	22 (53.7%)	$\chi^2 = 1.2$	2	0.55
HAM-D (M,SD)	31.8 (5.1)	31.6 (4.6)	32.0 (5.3)	31.6 (5.4)	F = 0.1	2	0.92
SRRS (M, SD)	28.1 (10.4)	29.7 (10.9)	27.1 (10.3)	27.5 (10.1)	F = 0.7	2	0.49
Episode Duration in weeks (M,SD)	36.0 (86.8)	42.7 (110.9)	25.6 (32.2)	40.4 (98.8)	F = 0.5	2	0.63
Use of benzodiazepines (N,%) ^b	93 (76.2%)	30 (76.9%)	32 (76.2%)	31 (75.6%)	$\chi^2 = 0.0$	2	0.99

HAM-D: total score Hamilton Depression Rating Scale.

SRRS: total score Salpetriere Retardation Rating Scale.

M = Mean SD= Standard deviation.

^a Testing for differences between treatment groups One-way ANOVA for continuous variables; χ^2 -tests for dichotomous variables.

^b Numbers of patients using benzodiazepines during treatment.

Table 2

Measures of psychomotor retardation at baseline and after 6 weeks of treatment ($n = 122$).

Categorical measures	Baseline		After 6 weeks ^a		χ^2	df	p-value
	N (%)	N (%)	N (%)	N (%)			
Clinical Retardation (SRRS>20)	89 (73.0%)	43 (35.2%)			13.6	1	<0.001
HAM-D retardation	67 (54.9%)	29 (23.8%)			31.2	1	<0.001
Dimensional measures	Mean	(SD)	Mean	(SD)	t	df	p-value
SRRS total score	28.1	10.4	16.8	(11.9)	11.4	121	<0.001
SRRS-6	8.6	5.4	5.2	(4.9)	8.3	121	<0.001

SRRS: Salpetriere Retardation Rating scale; HRI: HAM-D: Hamilton Rating Scale for Depression.

^a Last observation carried forward.

Table 3

Depressive symptoms, hallucinations and delusions at baseline and after 7 weeks of treatment (N = 122).

	Baseline	Follow up (7 weeks)	t	df	p-value
	HAM-D Mean (SD)	31.8 (5.1)	15.3 (10.6) ^{a/b}	17.2	121
	Baseline	Follow up (7 weeks)	Chi ²	df	p-value
Hallucinations N (%)	29 (23.8)	14 (11.5%) ^a	41.7	1	<0.001
Delusions N (%)	111 (91.0)	37 (30.3%) ^a	5.3	1	<0.03

HAM-D: Hamilton Rating Scale for Depression.

^a Last observation carried forward method.

^b Response $n = 62$ (50.8%); Remission $n = 37$ (30.3%).

Retardation (SRRS-6 score) and outcome measures after 7 weeks of treatment. Logistic regression analyses were adjusted for age, gender, baseline Hamilton score without retardation, antipsychotic medication before study start and treatment condition (imipramine, venlafaxine or venlafaxine plus quetiapine). Higher baseline SRRS-6 scores predicted significantly lower rates of HAM-D defined remission and higher persistence of delusions at follow up. The baseline SRRS-6 scores were not significantly associated with the other outcome measures (HAM-D defined response and hallucinations). Additional adjustment for depressive course characteristics (duration of the current episode and number of previous depressive episodes) did only slightly affect the results (for remission: $B = -0.082$ (SE = 0.045) $p = 0.066$; for delusions:

Table 4
Effects of baseline psychomotor retardation (SRRS-6 score) on the four outcome measures. Results of logistic regression analysis.

Predictor	Hamilton-response					Hamilton-remission						
	Beta	(SE)	Wald	df	p-value	Exp(B)	Beta	(SE)	Wald	df	p-value	Exp(B)
SRRS-6	-,012	,036	,111	1	,739	,988	-,085	,042	4,026	1	,045	,919

Predictor	Hallucinations after treatment					Delusions after treatment						
	Beta	(SE)	Wald	df	p-value	Exp(B)	Beta	(SE)	Wald	df	p-value	Exp(B)
SRRS-6	-,014	,061	,055	1	,815	,986	,108	,040	7,202	1	,007	1,114

All analyses based on last observation carried forward method. Analyses adjusted for age, gender, recent antipsychotic medication, baseline HAM-D score without retardation and treatment (imipramine, venlafaxine or venlafaxine plus quetiapine). SRRS: Salpetriere Retardation Rating Scale.

B = 0.118 (SE = 0.042) p = 0.005).

In a subsequent analysis we added the interaction terms of Psychomotor Retardation (baseline SRRS-6 score) and the three treatment conditions. The results are presented in Table 5. There were no significant effects for these retardation by treatment interactions on any of the outcome measures.

Finally we studied the effects of treatment condition on the outcome of psychomotor retardation (SRRS-6 score) in a multiple regression analysis adjusting for baseline SRRS-6 score, baseline HAM-D score without retardation, age and gender. For these analyses we only included patients with complete SRRS-6 scores at follow up (n = 103).

In the first analysis where imipramine was used as the reference, a significant positive effect was present for venlafaxine indicating higher retardation scores at follow up (B = 2.447 SE = 0.896 t = 2.73 p < 0.008). For treatment with venlafaxine plus quetiapine there was no significant effect compared to imipramine (B = 0.227 SE = 0.92 t = 0.254 p = 0.800).

Repeating the analysis using venlafaxine plus quetiapine as the reference we found a significant effect in the same direction for patients who were treated with venlafaxine (B = 5.972 SE = 2.330 t = 2.563 p < 0.05).

4. Discussion

Psychomotor disturbance covers a group of clinical characteristics which can be observed and objectively measured (van Diermen et al., 2018). It can be used for subtyping of disorders, and refers to the dysfunction of underlying neurobiological pathways (Walther et al., 2019).

For unipolar depression Psychomotor Retardation has been identified as a severity marker which may also influence treatment choice.

The present study investigates Psychomotor Retardation in a sample of well characterized patients with unipolar Psychotic Depression during the course of antidepressant pharmacological treatment. The main findings are:

1. Clinical levels of Psychomotor Retardation were present in a large majority of the patients at baseline and remitted in more than 50% of the patients during treatment.
2. Baseline Psychomotor Retardation predicted lower depression remission rates in addition to higher persistence of delusions.
3. Patients using venlafaxine retained higher Psychomotor Retardation scores at follow-up compared to patients who were treated with imipramine or venlafaxine plus quetiapine.

4.1. Prevalence and course of psychomotor retardation during treatment

At baseline, 73% of the patients showed clinical levels of Psychomotor Retardation. This rate is in agreement with earlier studies. Parker et al. (1991) observed signs of retardation in about 75% of patients with Psychotic Depression compared to percentages below 50% in patients with endogenous depression and melancholic depression. In another sample, patients with Psychotic Depression presented higher rates of Psychomotor Retardation compared to patients with melancholic depression (Parker et al., 1997). Several other studies report high levels of Psychomotor Retardation in Psychotic Depression compared to non-psychotic depression (Coryell et al., 1984; Lattuada et al., 1999; Schatzberg and Rothschild, 1992).

During treatment we observed a 30–40% reduction of Psychomotor Retardation according to both categorical and dimensional measures. This suggests that in a large proportion of the patients Psychomotor Retardation can be considered a state characteristic, which is in agreement with the literature regarding non-psychotic depressed patients (Schrijvers et al., 2008).

There was no age difference with respect to Psychomotor Retardation in our patients. Although, in general, elderly patients are at an increased risk for Psychomotor Retardation (Brodaty et al., 1997; Schrijvers et al., 2008), the absence of an observable association in our sample may be related to exclusion of patients over 65 years of age. The observed lack of a gender difference in Psychomotor Retardation is in

Table 5
Effects of drug - retardation interactions on the four outcome measures after 7 weeks of treatment. Results of logistic regression analysis.

Interaction term	Hamilton-response					Hamilton-remission						
	Beta	(SE)	Wald	df	p-value	Exp(B)	Beta	(SE)	Wald	df	p-value	Exp(B)
Imipramine *SRRS-6	,023	,085	,071	1	,790	1,023	,054	,101	,284	1	,594	1,055
Venlafaxine *SRRS-6	,014	,097	,020	1	,888	1,014	,114	,105	1164	1	,281	1,121

Interaction term	Hallucinations after treatment					Delusions after treatment						
	Beta	(SE)	Wald	df	p-value	Exp(B)	Beta	(SE)	Wald	df	p-value	Exp(B)
Imipramine*SRRS-6	,032	,160	,040	1	,841	1,033	,111	,104	1,132	1	,287	1,117
Venlafaxine*SRRS-6	,000	,157	,000	1	,999	1,000	,047	,108	,192	1	,661	1,048

All analyses based on last observation carried forward method. Analyses adjusted for age, gender, recent antipsychotic medication, baseline HAM-D score without retardation, retardation (SRRS-6 score) and treatment (imipramine, venlafaxine). Venlafaxine plus quetiapine treatment and the interaction term of venlafaxine + quetiapine*SRRS-6 served as reference variables.

SRRS: Salpetriere Retardation Rating Scale.

accordance to the literature (Schrijvers et al., 2008).

4.2. Associations with baseline clinical variables

Associations between Psychomotor Retardation and the number of previous depressive episodes are in agreement with the observations of Calugi et al. (2011) and Gorwood et al. (2014) in non-psychotic depressed patients, but have not been demonstrated in patients with Psychotic Depression before. As both severity and recurrence of depression are markers of familial occurrence (Janzing et al., 2009), Psychomotor Retardation may be an expression of genetic liability. In agreement, Parker (2000) reported that psychomotor disturbance, especially presenting at young age, is associated with a positive family history of depression. Alternatively, according to the scarring hypothesis of Gorwood et al. (2014), Psychomotor Retardation may be the consequence of experiencing previous depressive episodes. To answer the question on the direction of association, prospective studies are necessary.

4.3. Associations with treatment outcome

Considering the outcome of treatment in Psychotic Depression, both depressive symptoms and psychotic symptoms should be taken into account. (Østergaard et al., 2014). The observation that higher baseline Psychomotor Retardation levels predict lower HAM-D remission rates is in accordance with studies in patients with non-psychotic depression (Calugi et al., 2011; Gorwood et al., 2014), but has not been reported before in patients with Psychotic Depression. As the attainment of remission decreases the risk for relapse, Psychomotor Retardation can be considered a negative predictor for the long term course of Psychotic Depression. Baseline levels of Psychomotor Retardation did not affect the HAM-D defined response rate. We can speculate about the reason why higher baseline retardation scores predicted lower rates of remission while no significant effect on response was found. The increasing association between Psychomotor Retardation and HAM-D symptoms during treatment (correlations rising from 0.28 (baseline) to 0.56 (6 weeks)) suggests that depression symptoms unrelated to retardation are more responsive to treatment than retardation related symptoms. Given the low baseline correlation between retardation and depressive symptoms, we can assume that also in patients with higher baseline retardation scores the majority of baseline depressive symptoms is unrelated to retardation (responsive to treatment). Therefore they can easily reach substantial symptom reductions (response). However especially in these patients substantial levels of the unresponsive retardation related depressive symptoms may persist, reducing their probability of reaching remission.

In addition, higher baseline Psychomotor Retardation levels were associated with the persistence of delusions after treatment. Also this observation has not been reported before. It can be appreciated in the context of earlier observations taking different levels of explanation into account. At the neuropsychological level, the neurocognitive symptoms associated with Psychomotor Retardation including deficits in executive functions, speed of processing and verbal memory may interfere with reality testing (Guillem et al., 2008). At the biological level both psychotic symptoms and Psychomotor Retardation may reflect disturbances in dopaminergic neurotransmission. For depression, neurobiological research suggests that Psychomotor Retardation is associated with abnormalities in connections between cortical and subcortical brain structures and altered dopaminergic neurotransmission (Buyukdura et al., 2011; Schrijvers et al., 2008). Finally at the syndromic level Psychomotor Retardation co-occurs with psychotic symptoms in several neuropsychiatric disorders including schizophrenia, delirium and Parkinson's disease. Also for these disorders functional and/or structural alterations in dopaminergic pathways play an important role in their pathophysiology.

4.4. Associations with antidepressant pharmacotherapy

In nonpsychotic unipolar depression, the presence of Psychomotor Retardation has been associated with a poor response to antidepressant pharmacotherapy, especially with respect to SSRI's (Schrijvers et al., 2008; Ulbricht et al., 2018)). We did not observe differences between treatment strategies (imipramine, venlafaxine or venlafaxine plus quetiapine) regarding the outcome of depression and positive psychotic symptoms. However, patients treated with venlafaxine had significantly higher scores of retardation at follow up compared to patients treated with imipramine or venlafaxine plus quetiapine. Interestingly, these findings partly parallel those of the primary study (Wijkstra et al., 2010) where venlafaxine plus quetiapine was also found superior to venlafaxine alone with respect to treatment response. This result was unexpected as according to the literature most of the dual acting antidepressants are thought to have beneficial effects on psychomotor retardation. It may be of clinical importance regarding the association of psychomotor retardation with treatment resistance in addition to several other characteristics indicating a more severe course of depression.

Our study has a number of strengths:

Patients were well characterized and constitute one of the largest samples with Psychotic Depression studied to date. A large number of potential confounders have been taken into account:

- Except study medication, participants were not allowed to use psychotropic drugs apart from low doses of benzodiazepines.
- Patients with severe somatic or neurological disorders or substance use were excluded from participation thereby limiting the possibility that Psychomotor Retardation was a consequence of these disorders.
- Associations between Psychomotor Retardation and outcome were adjusted for clinical and demographic characteristics (age, gender and recent antipsychotic use) which may be associated with Psychomotor Retardation levels.

A limitation is that we used separate outcome variables for depressive and psychotic symptoms whereas the recently developed Psychotic Depression Assessment Scale (PDAS) allows to take both symptom groups into account (Østergaard et al., 2014).

5. Conclusion

This study contributes to the literature by presenting several new findings regarding the role of Psychomotor Retardation in patients with unipolar Psychotic Depression. Combining its high prevalence and its predictive value for treatment outcome (lower remission rates and higher rates of delusions at follow up), we conclude that Psychomotor Retardation is a severity marker also in patients with Psychotic Depression. The results of this study can be generalized to other patients aged 18–65 years with a diagnosis of unipolar Psychotic Depression as our sample was recruited from a multi-centre study and the study was performed in the context of regular clinical patient care.

Contributors

The study was initiated by Nolen WA.

Design and study protocol: Nolen WA in cooperation with all the other authors.

All authors participated in the data collection.

Drafting of the manuscript: Janzing JGE and Verkes RJ.

Statistical Analysis: Janzing JGE.

Interpretation of the results: Janzing JGE and Verkes RJ.

Critical revision of the manuscript: all authors.

All authors have approved the final manuscript.

Declaration of competing interest

The following authors declare no conflicts of interest: Dr. Janzing, Dr. van den Broek, Dr. Breteler and Dr. Verkes.

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References

- American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR. American Psychiatric Association, Washington D.C.
- American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, fifth ed. American Psychiatric Publishing, Arlington, VA.
- Brebion, G., Smith, M.J., Widlocher, D., 1997. Discrimination and response bias in memory: effects of depression severity and psychomotor retardation. *Psychiatr. Res.* 70 (2), 95–103.
- Brodaty, H., Luscombe, G., Parker, G., Wilhelm, K., Hickie, I., Austin, M.P., Mitchell, P., 1997. Increased rate of psychosis and psychomotor change in depression with age. *Psychol. Med.* 27 (5), 1205–1213.
- Buyukdura, J.S., McClintock, S.M., Croarkin, P.E., 2011. Psychomotor retardation in depression: biological underpinnings, measurement, and treatment. *Progress in neuro-psychopharmacology & biological psychiatry* 35 (2), 395–409.
- Calugi, S., Cassano, G.B., Litta, A., Rucci, P., Benvenuti, A., Miniati, M., Lattanzi, L., Mantua, V., Lombardi, V., Fagioli, A., Frank, E., 2011. Does psychomotor retardation define a clinically relevant phenotype of unipolar depression? *J. Affect. Disord.* 129 (1–3), 296–300.
- Coryell, W., Pfuhl, B., Zimmerman, M., 1984. The clinical and neuroendocrine features of psychotic depression. *J. Nerv. Ment. Dis.* 172 (9), 521–528.
- Dantchev, N., Widlocher, D.J., 1998. The measurement of retardation in depression. *J. Clin. Psychiatr.* 59 (Suppl. 14), 19–25.
- de Weme, R.J., Hoeksema, T., Goekoop, J.G., 1996. De widlocher remmingschaal, een nederlandse schaal voor het meten van Psychomotorische remming. *Acta Neuropsychiatr.* 8 (3), 56–63.
- First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1999. Structured Clinical Interview for DSM-IV axis I Disorders. (Dutch Translation). Swets&Zeitlinger, Lisse, the Netherlands.
- Gorwood, P., Richard-Devantoy, S., Bayle, F., Clery-Melin, M.L., 2014. Psychomotor retardation is a scar of past depressive episodes, revealed by simple cognitive tests. *Eur. Neuropsychopharmacol. : the journal of the European College of Neuropsychopharmacology* 24 (10), 1630–1640.
- Guillem, F., Rinaldi, M., Pampoulova, T., Stip, E., 2008. The complex relationships between executive functions and positive symptoms in schizophrenia. *Psychol. Med.* 38 (6), 853–860.
- Hamilton, M., 1960. A rating scale for depression. *J. Neurol. Neurosurg. Psychiatr.* 23, 56–62.
- Heijnen, W., Kamperman, A.M., Tjokrodipo, L.D., Hoogendijk, W.J.G., van den Broek, W. W., Birkenhager, T.K., 2019. Influence of age on ECT efficacy in depression and the mediating role of psychomotor retardation and psychotic features. *J. Psychiatr. Res.* 109, 41–47.
- Hickie, I., Mason, C., Parker, G., Brodaty, H., 1996. Prediction of ECT response: validation of a refined sign-based (CORE) system for defining melancholia. *Br. J. Psychiatry* 169 (1), 68–74.
- Janzing, J.G., de Graaf, R., ten Have, M., Vollebergh, W.A., Verhagen, M., Buitelaar, J.K., 2009. Familiarity of depression in the community; associations with gender and phenotype of major depressive disorder. *Soc. Psychiatr. Psychiatr. Epidemiol.* 44 (12), 1067–1074.
- Lampe, I.K., Kahn, R.S., Heeren, T.J., 2001. Apathy, anhedonia, and psychomotor retardation in elderly psychiatric patients and healthy elderly individuals. *J. Geriatr. Psychiatr. Neurol.* 14 (1), 11–16.
- Lattuada, E., Serretti, A., Cusin, C., Gasperini, M., Smeraldi, E., 1999. Symptomatologic analysis of psychotic and non-psychotic depression. *J. Affect. Disord.* 54 (1–2), 183–187.
- Novick, J.S., Stewart, J.W., Wisniewski, S.R., Cook, I.A., Manev, R., Nierenberg, A.A., Rosenbaum, J.F., Shores-Wilson, K., Balasubramani, G.K., Biggs, M.M., Zisook, S., Rush, A.J., investigators, S.D., 2005. Clinical and demographic features of atypical depression in outpatients with major depressive disorder: preliminary findings from STAR*D. *J. Clin. Psychiatr.* 66 (8), 1002–1011.
- Østergaard, S.D., Meyers, B.S., Flint, A.J., Mulsant, B.H., Whyte, E.M., Ulbricht, C.M., Bech, P., Rothschild, A.J., 2014. Measuring treatment response in psychotic depression: the Psychotic Depression Assessment Scale (PDAS) takes both depressive and psychotic symptoms into account. *J. Affect. Disord.* 160, 68–73.
- Parker, G., 2000. Classifying depression: should paradigms lost be regained? *Am. J. Psychiatr.* 157 (8), 1195–1203.
- Parker, G., Hadzi-Pavlovic, D., Hickie, I., Boyce, P., Mitchell, P., Wilhelm, K., Brodaty, H., 1991. Distinguishing psychotic and non-psychotic melancholia. *J. Affect. Disord.* 22 (3), 135–148.
- Parker, G., McCraw, S., 2017. The properties and utility of the CORE measure of melancholia. *J. Affect. Disord.* 207, 128–135.
- Parker, G., Roussos, J., Mitchell, P., Wilhelm, K., Austin, M.P., Hadzi-Pavlovic, D., 1997. Distinguishing psychotic depression from melancholia. *J. Affect. Disord.* 42 (2–3), 155–167.
- Schatzberg, A.F., Rothschild, A.J., 1992. Psychotic (delusional) major depression: should it be included as a distinct syndrome in DSM-IV? *Am. J. Psychiatr.* 149 (6), 733–745.
- Schrijvers, D., Hulstijn, W., Sabbe, B.G., 2008. Psychomotor symptoms in depression: a diagnostic, pathophysiological and therapeutic tool. *J. Affect. Disord.* 109 (1–2), 1–20.
- Smith, M.J., Brebion, G., Banquet, J.P., Allilaire, J.F., 1994. Experimental evidence for two dimensions of cognitive disorders in depressives. *J. Psychiatr. Res.* 28 (4), 401–411.
- Sobin, C., Sackeim, H.A., 1997. Psychomotor symptoms of depression. *Am. J. Psychiatr.* 154 (1), 4–17.
- SPSS IBM Corp, 2017. IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY).
- Ulbricht, C.M., Dumenci, L., Rothschild, A.J., Lapane, K.L., 2018. Changes in depression subtypes among men in STAR*D: a latent transition analysis. *Am. J. Men's Health* 12 (1), 5–13.
- van Diermen, L., Vanmarcke, S., Walther, S., Moens, H., Veltman, E., Fransen, E., Sabbe, B., van der Mast, R., Birkenhager, T., Schrijvers, D., 2019. Can psychomotor disturbance predict ect outcome in depression? *J. Psychiatr. Res.* 117, 122–128.
- van Diermen, L., Walther, S., Cools, O., Fransen, E., Birkenhager, T.K., Sabbe, B.C.G., Schrijvers, D., 2018. Observer-rated retardation but not agitation corresponds to objective motor measures in depression. *Acta Neuropsychiatr.* 30 (6), 359–364.
- Walther, S., Bernard, J.A., Mittal, V.A., Shankman, S.A., 2019. The utility of an RDoC motor domain to understand psychomotor symptoms in depression. *Psychol. Med.* 49 (2), 212–216.
- Widlocher, D.J., 1983. Psychomotor retardation: clinical, theoretical, and psychometric aspects. *Psychiatr. Clin.* 6 (1), 27–40.
- Wijksta, J., Burger, H., van den Broek, W.W., Birkenhager, T.K., Janzing, J.G., Boks, M. P., Bruijn, J.A., van der Loos, M.L., Breteler, L.M., Ramaekers, G.M., Verkes, R.J., Nolen, W.A., 2010. Treatment of unipolar psychotic depression: a randomized, double-blind study comparing imipramine, venlafaxine, and venlafaxine plus quetiapine. *Acta Psychiatr. Scand.* 121 (3), 190–200.