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Research report

# Does early improvement triggered by antidepressants predict response/remission? — Analysis of data from a naturalistic study on a large sample of inpatients with major depression☆

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**Abstract**

*Background:* Delayed onset of efficacy of antidepressants and a high proportion of depressed patients being poor or non-responders to antidepressants are well known clinical challenges. Therefore, it seems to be necessary to identify predictors for response and – even more important – for remission. It has been suggested that reduction of depressive symptoms at an early stage of antidepressant treatment may predict treatment outcome. Our objective was to test, if this hypothesis derived from randomized controlled studies (RCTs) in outpatients, would be confirmed in a large naturalistic study in a cohort of inpatients with major depression. Patients were treated with various antidepressants and co-medication according to the protocol based on evidence-based clinical guidelines.

*Methods:* This was a large naturalistic prospective study. All patients ($N$=795) were hospitalized and met DSM-IV criteria for major depression according to a structured clinical interview (SCID). Assessments were conducted biweekly. Several definitions of early improvement (20%, 25% and 30% reduction in HAMD-21 baseline total scores) at two different visits were tested. Sensitivity, specificity and predictive values were calculated for the different definitions of early improvement. ROC-analyses as

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well as logistic regression models have been performed. Response was defined as 50% improvement of the total baseline HAMD-21 score and remission as a score of ≤7 at discharge. Additionally, time to response was analyzed by computing Kaplan–Meier survival estimates for the "best" early improvement definition in comparison to non early improvement. Subgroup analyses were conducted to test whether the results were consistent across treatment subgroups.

*Results:* 48.8% of patients in our sample were remitters. The overall response rate was 79.6%. A 20% reduction of HAMD-21 total baseline score at Day 14 provided a sensitivity of 75% and a specificity of 59% for response prediction. This definition of early improvement was an even more sensitive predictor for remission (80%) with a limited specificity (43%). The AUC value of about 0.68 for early response (20% improvement) indicates good predictability for both time intervals tested (Day 14 and Day 28) and changed only marginally with increased percentages in score reduction (AUC=0.71 and 0.73, respectively). More than one third (37%) of all patients who had not improved at Day 14 showed not response in the later treatment course (this was the case for nearly half of all patients (43%) at Day 28).

Similar results were obtained by Kaplan–Meier survival analyses. Log-rank test showed significantly longer time to response in patients with non-early improvement ($p<0.0001$).

*Limitations:* Results were assessed by a post-hoc analysis based on prospectively collected data. Several caveats of a naturalistic design must be mentioned, especially there was no control group and only a limited number of stratification factors could be considered.

*Conclusion:* The results support earlier findings that early improvement in the first two weeks may predict with high sensitivity later response and remission, even in hospitalized patients suffering from a more severe degree of depression. Since we used a naturalistic study design, the data may be considered as a replication of previous results drawn from RCTs in a naturalistic environment. We found a global antidepressant effect which was consistent across treatment subgroups regarding sensitivity values. However, we are aware of the inability of effectiveness studies to draw causal treatment relationships from the uncontrolled approach. Nevertheless, the replication of previous results might indicate that a drug switch during treatment in case of lack of early improvement could be accelerated.

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*Keywords:* Depression; Naturalistic design; Early improvement; Response; Remission; Prediction

## 1. Introduction

Obviously, a variety of components contribute to antidepressant response resulting in difficulties in disentangling the determinants. Various clinical features have been proposed as predictors (Hirschfeld et al., 1998; Kozel et al., 2008; Trivedi et al., 2006). Predicting treatment outcome *at an early stage* is of major relevance. Quitkin et al. (1987, 1996) have proposed that onset of drug response occurs after three to four weeks of treatment. Other authors emphasized that even an earlier onset after two weeks was highly predictive of later outcome (Nierenberg et al., 1995; Nierenberg et al., 2000; Nierenberg, 2003; Stassen et al., 1996; Szegedi et al., 2003). All these findings were derived from clinical studies, either randomized, placebo-controlled (Stassen et al., 1996; Szegedi et al., 2003) or open trials (Nierenberg et al., 1995). Szegedi et al. (2003) replicated the results described by Stassen et al. (1993, 1996) as well as Nierenberg et al. (1995) using a different methodological approach. Mainly sensitivity, specificity, predictive values and AUC values were calculated, whereas the other authors used survival analyses. However, Szegedi et al. (2003) mentioned several important limitations of their results: 1. They only investigated patients with mild to moderate severity. 2. Various restrictions concerning co-medication and co-morbidities may limit generalizability of the results. 3. Only two different antidepressant compounds (mirtazapine/paroxetine) were tested (Szegedi et al., 2003). Nierenberg et al. (1995) also investigated only one single compound (fluoxetine). Stassen et al. (1993, 1996) analyzed four compounds in a larger dataset . We tried to overcome the above mentioned limitations at the expense of other caveats, described in detail in our discussion. Our main aim was to investigate whether or not early improvement was a valid predictor of later response or remission in a cohort of depressed inpatients during ongoing treatment with antidepressants. In detail, our main objectives were:

1. To test systematically different definitions of early improvement in terms of different baseline score reductions using the 21-item Hamilton Depression Rating Scale (HAMD-21) (Hamilton, 1967) after 14 or 28 days (20%, 25%, 30% reduction).
2. To determine sensitivity and specificity values for early improvement as a predictor for response or remission, respectively, using the results of the above mentioned first objective regarding different cut-offs for early improvement.
3. To determine the areas under the ROC-curves in order to estimate the most appropriate predictor.

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