*Short Report*

# Early improvement as a predictor of treatment response and remission in patients with schizophrenia: A pooled, post-hoc analysis from the asenapine development program

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**Abstract**

**Objective:** The purpose of this study was to assess whether early symptom improvement predicts later treatment outcome in patients with schizophrenia.

**Methods:** Data were pooled from intent-to-treat (ITT) populations of three six-week randomized controlled studies with fixed doses of asenapine (ASE; *n*=470), olanzapine (OLA; *n*=95), risperidone (RIS; *n*=56), haloperidol (HAL; *n*=112), or placebo (PLA; *n*=275). Early improvement was defined as a 20% reduction of Positive and Negative Syndrome Scale (PANSS) total score at week 2, compared to baseline (primary criterion). Treatment outcome at week 6 was defined as response (PANSS: ≥50% score reduction) or remission (PANSS item score ≤3 on selected items at week 6). Odds ratios (ORs) and predictive performance statistics were calculated.

**Results:** Statistically significant associations between early improvement (at week 2) and treatment outcome (at week 6) were observed for all treatment groups except OLA; as evidenced by increased ORs for response. Analysis of associations between early improvement and remission, as defined by Andreasen et al. (2005), revealed a statistically significant relationship for ASE and PLA-treated patients only. Predictive performance statistics revealed higher negative predictive value (NPV) and sensitivity rates, and comparably lower positive predictive value (PPV) and specificity rates across treatment groups for both response and remission.

**Conclusion:** It is suggested that absence of improvement within two weeks of treatment may predict the unlikely success of subsequent pharmacological intervention.

**Keywords**

Schizophrenia, antipsychotics, early improvement predictor of treatment outcome, response, remission, asenapine

## Introduction

Large meta-analyses (Agid et al., 2003, Leucht et al., 2005a) have rejected a long-held belief that there is a delay of onset of action of antipsychotic drugs in schizophrenia. Rather, it seems that antipsychotics begin acting immediately, and that their effects can be disentangled from that of placebo (PLA) as early as 24 h after initiation of treatment (Agid et al., 2008; Kapur et al., 2005). These findings consequently have implications for treatment decisions. For as long as psychiatrists believed that antipsychotic drugs only started to act after several weeks of treatment, understandably guidelines had to recommend to evaluate a treatment for at least several weeks (in some cases up to 6–8 weeks (World Federation of Societies of Biological Psychiatry (WFSBP) guidelines; Falkai et al., 2005) before it should be considered ineffective and major changes in treatment implemented. The early onset concept of antipsychotic drug action, however, suggests that it might be predicted already after one or two weeks of treatment whether patients will respond to a given drug or not. Several previous studies proposed such a hypothesis, however these studies were correlational in nature and cut-offs were not provided, limiting the clinically usable indicators of future nonresponse (Bartko et al., 1987; Nedopil et al., 1983; Stern et al., 1993; Zemlan et al., 1990). More recently, a number of studies have tried to develop diagnostic tests, in terms of sensitivity and specificity, to predict later response using the early improvement to an antipsychotic (Ascher-Svanum et al., 2008; Chang et al., 2006; Correll et al., 2003; Leucht et al., 2007a). However, these analyses were hampered by various limitations such as small sample sizes, arbitrary choice of studies, or post-hoc definition of cut-offs.

In this context, the current paper presents an early prediction analysis using all the pivotal studies from the asenapine (ASE) development program in acute schizophrenia, with fixed dose ASE. ASE is an antipsychotic agent indicated in the United States, Australia, Canada and other countries outside the European Union for treatment of adults with schizophrenia and as monotherapy or adjunctive therapy with lithium or valproate;

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in the treatment of manic or mixed episodes associated with bipolar I disorder and in the European Union for the treatment of moderate to severe manic episodes associated with bipolar I disorder. The present analyses aims to predict later response/non-response and remission/non-remission by early improvement/non-improvement using a priori defined definitions, as evidenced by previous analyses (Kinon et al., 2010; Leucht et al., 2008), rather than post-hoc findings (Leucht et al., 2006). The results could provide important answers to the question of how long the antipsychotic drugs examined should be tested, before being considered ineffective and switched.

## Methods

### Study design

A post-hoc analysis was performed on pooled individual subject data from three multinational, six-week, phase 3 studies that compared fixed-dose ASE ($n$=470), olanzapine (OLA; $n$=95), risperidone (RIS; $n$=56), haloperidol (HAL; $n$=112) with PLA ($n$=275) in patients with schizophrenia in an acutely exacerbated state (Trial 1: Potkin et al., 2007, trial 2: NCT00156117, trial 3 NCT00156104 & Kane et al., 2010). A fourth multinational six-week phase 3 study (NCT00151424/HERA41022), using a flexible dosing regimen, was not included in the present analysis. All trials are from the ASE late stage schizophrenia development program and are very similar in design with respect to trial duration, fixed-dose regimen, PLA-controlled, baseline characteristics etc. Briefly, the trials included adult patients who met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition - Text Revised* (DSM-IV-TR) criteria for primary diagnosis of schizophrenia of the paranoid type, disorganized type, catatonic type, or undifferentiated type. The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) was used by the participating clinicians to assess the severity of schizophrenic symptoms. Subjects were required to have a PANSS score of at least 60 at screening and baseline (the baseline PANSS score could not have been ≥20% lower than the screening PANSS score); a score of at least four on two or more of the five items of the positive subscale of the PANSS at screening and baseline; and a Clinical Global Impression-Severity scale (CGI-S; Guy, 1976) score at least four ("moderately ill") at baseline. Patients were also required to have had a positive response to an antipsychotic medication other than clozapine, discontinued any depot neuroleptics prior to baseline, and provided written informed consent. Participants were excluded from the trial if they met DSM-IV-TR diagnostic criteria for schizophrenia of residual subtype or schizoaffective disorder, or had a concurrent Axis I psychiatric disorder other than schizophrenia or a primary diagnosis other than schizophrenia. The average baseline PANSS total scores and CGI-S scores were similar across the three studies.

### Treatment

Patients were randomized to six weeks of double-blind PLA (sublingual + oral), sublingual ASE (5 or 10 mg) + oral PLA, oral OLA (15 mg) + sublingual PLA, oral RIS (3 mg) + sublingual PLA, or oral HAL (4 mg) + sublingual PLA. In trial 1 (Potkin et al., 2007), subjects randomized to the 5 mg twice daily ASE group received trial medication according to the following schedule: 1 mg twice daily on Day 1; 2 mg twice daily on Day 2; 3 mg twice daily on Day 3; 4 mg twice daily on Day 4; and 5 mg twice daily on Days 5 through 42. In the other trials (NCT00156117; NCT00156104 & Kane et al., 2010), subjects randomized to the ASE 5 mg group received 5 mg twice daily for six weeks. Subjects randomized to the ASE 10 mg group received two doses of ASE 5 mg on day 1, and 10 mg twice daily for the remainder of the six-week trial. Subjects randomized to the OLA 15 mg group received 10 mg once daily (at approximately 08:00) during the first seven days of the double-blind treatment period, and 15 mg once daily (at approximately 08:00) for the remainder of the six-week trial (NCT00156117). Subjects randomized to the RIS 3 mg twice daily group (Potkin et al., 2007) received two doses of RIS 1 mg on day 1, two doses of RIS 2 mg on day 2, and 3 mg twice daily for the remainder of the six-week trial. Subjects randomized to HAL (Kane et al., 2010) received 4 mg twice daily for six weeks. Twice daily dosing of treatments was conducted at approximately 08:00 and 20:00.

### Outcome measures

The primary criterion of all studies was change in PANSS total score from baseline. Assessments using PANSS were performed at screening, baseline, and on treatment days 4 (trials NCT00156117/HERA41021 and NCT00156104/HERA41023/Kane et al., 2010), 7, 14, 21, 28, 35 and 42 (trials Potkin at al., 2007, NCT00156117/HERA41021 and NCT00156104/HERA41023/Kane et al., 2010).

For the purpose of the post-hoc analysis, the following patient groups were a priori defined:

(a) Early improvers: a reduction from baseline in total score of ≥20% (cut-off point; primary criterion) assessed at day 14. Two weeks was chosen as this is a time point that allowed for prediction in previous studies (Ascher-Svanum et al., 2008; Kinon et al., 2010; Ruberg et al., 2011; Stauffer et al., 2011). Moreover, in clinical practice, drugs are often titrated slowly, therefore treatment decisions before two weeks would often not be appropriate.
(b) Treatment responders: a reduction from baseline in total score ≥50% at week 6. Various equipercentile linking analyses have shown that this cut-off roughly corresponds to "much improved" according to the CGI-S (Guy, 1976) judgment of raters and is therefore clinically meaningful.
(c) Treatment remitters: a PANSS score of ≤3 on items P1, G9, P3, P2, G5, N1, N4 and N6 at week 6 (Andreasen et al., 2005).

The calculation of percentage response was corrected by subtraction of the 30 points minimum PANSS total score from the baseline score (Leucht et al., 2007b, 2009a, b; Obermeier et al., 2010).

### Statistical analyses

Predictive value of early improvement for later response or remission at week 6 was performed on the intent-to-treat (ITT) population. Patients with missing values were considered as

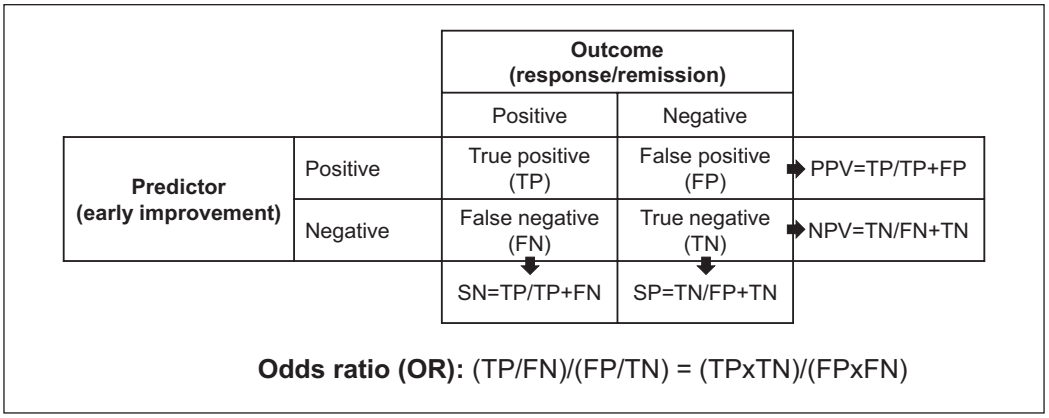


**Figure 1.** A schematic overview of predictive performance variables and their relationship to early improvement and treatment outcome. NPV: negative predictive value; PPV: positive predictive value; SN: sensitivity; SP: specificity.

treatment failures at week 6, i.e. not response, or not remission. The number of early improvers, responders, or remitters assessed using PANSS were entered into a contingency table and the association between early improvement (visit day 14) and treatment response or remission at week 6 was assessed using odds ratios (ORs; Figure 1) with 95% confidence intervals (CIs). The *p*-values were calculated using a Fischer's Exact Test. No adjustments were made for multiplicity. Predictive performance statistics were calculated for each treatment group (Figure 1) using a 20% early response cut-off value, as identified in previous analyses (Ascher-Svanum et al. 2008; Jager et al., 2009; Kinon et al., 2008, 2010). They included the following:

(1) Sensitivity (SN): (early improvers who became later responders or remitters/all patients who became later responders or remitters)×100
(2) Specificity (SP): (early non-improvers who did not become later responders or remitters/all patients who did not become later responders or remitters)×100
(3) Positive predictive value (PPV): (early improvers who became later responders or remitters/all improvers)×100
(4) Negative predictive value (NPV): (early non-improvers who did not become later responders or remitters/all non-improvers)×100

The analyses were not intended to make any comparative claims of efficacy across treatments due to the nature of the primary trials and the relatively small sample size of patients on active comparators versus ASE. All treatments were not pooled to allow for differences in effect of individual treatments.

All statistical analyses were performed using SAS analytical software (SAS Institute Inc., Cary, North Carolina, USA).

## Results

Patient characteristics of two of the three primary studies included in the present analyses have been published elsewhere (Kane et al., 2010; Potkin et al., 2007). Briefly, baseline clinical characteristics were comparable between the treatment groups within each study and in the pooled dataset. Of the 1008 patients (male: 65.6%, female: 34.4%) included in the present pooled analyses, 470 patients (46.6%) were treated with ASE, 275 (27.3%) with PLA, 56 (5.6%) with RIS, 95 (9.5%) with OLA, and 112 (11.1%) with HAL. Most patients were aged 18–64 years (98.9%), and over half were Caucasian (52.4%); with the remainder of patients being Black (36.8%), Asian (5.0%), or other ethnicity (7.8%). The average PANSS total scores at baseline were comparable across treatment groups (ASE: 91.7, PLA: 91.6, RIS: 92.2, OLA: 93.7, HAL: 88.6) (see Table 1).

### *Early improvement using PANSS total scores*

Early improvement occurred in a substantial percentage of patients in the pooled population at week 2 (Figure 2). In the ASE treatment group, early improvement in PANSS total scores (≥20% cut-off) was evident in 40.6% of treated patients. Other treatment groups followed a similar pattern of improvement when assessed at week 2 (PLA: 35.3%, RIS: 33.9%, OLA: 34.7%, HAL: 46.4%).

### *Associations and predictive value of early improvement and treatment response using PANSS total scores*

ORs were calculated to assess whether early improvement as measured by PANNS at week 2 (i.e. ≥20% reduction in total score), was associated with a higher likelihood of subsequent treatment response at week 6 (i.e. ≥50% reduction in PANNS total score). Results showed that statistically significant associations between early improvement and response at week 6 were observed for all treatment groups except OLA; as evidenced by increased ORs for response (ASE: 6.76, $p<0.0001$; PL: 12.59, $p<0.0001$; RIS: 10.71, $p<0.05$; OLA: 3.84, $p=0.0528$; HAL: 8.89, $p<0.01$; Figure 3).

Predictive performance statistics revealed high NPV (ASE: 93.2%, PLA: 96.4%, RIS: 96.8%, OLA: 92.3%, HAL: 95.2%), and sensitivity (ASE: 80.8%, PLA: 86.1%, RIS: 83.3%, OLA: 66.7%, HAL: 88.9%) rates, and comparably lower PPV (ASE: 33.0%, PLA: 32.0%, RIS: 26.3%, OLA: 24.2%, HAL: 30.8%), and specificity (ASE: 61.7%, PLA: 67.0%, RIS: 68.2%, OLA: 65.8%, HAL: 52.6%) rates across treatment groups for treatment response (Figure 4).

**Table 1.** Outline of individual studies.

| | TRIAL | | |
|---|---|---|---|
| | Potkin et al., 2007 | NCT00156117 | NCT00156104/Kane et al., 2010 |
| **Treatments** | ASE (5 mg, BID)<br>RIS (3 mg, BID)<br>PLA (BID) | ASE (5 or 10 mg, BID)<br>OLA (15 mg, QD)<br>PLA (QD/BID) | ASE (5 or 10 mg, BID)<br>HAL (4 mg, BID)<br>PLA (BID) |
| **ITT sample size (*n*)** | ASE=58<br>RIS=56<br>PLA=60 | ASE (5 mg)=102<br>ASE (10 mg)=96<br>OLA=95<br>PLA=93 | ASE (5 mg)=109<br>ASE (10 mg)=105<br>HAL=112<br>PLA=122 |
| **PANSS total score at baseline (mean (SE))** | ASE=96.48 (2.16)<br>RIS=92.18 (2.05)<br>PLA=92.43 (1.93) | ASE (5 mg)=90.8 (1.02)<br>ASE (10 mg)=93.2 (1.06)<br>OLA=92.6 (1.07)<br>PLA=93.7 (1.06) | ASE (5 mg)=88.9 (0.97)<br>ASE (10 mg)=89.4 (0.99)<br>HAL=88.5 (0.96)<br>PLA=89.0 (0.92) |
| **Change from baseline PANSS (mean (SE)); day 42)** | ASE= −15.86 (2.62)<br>RIS= −10.93 (2.67)<br>PLA= −5.27 (2.30) | ASE (5 mg)= −14.4 (1.58)<br>ASE (10 mg)= −13.5 (1.63)<br>OLA= −16.5 (1.64)<br>PLA= −11.1 (1.63) | ASE (5 mg)= −16.2 (1.65)<br>ASE (10 mg)= −14.7 (1.68)<br>HAL= −15.6 (1.62)<br>PLA= −10.8 (1.56) |

ASE: asenapine; BID: twice daily; HAL: haloperidol; ITT: intent-to-treat; OLA: olanzapine; PANSS: Positive and Negative Syndrome Scale; PLA: placebo; QD: once daily; RIS: risperidone; SE: standard error.

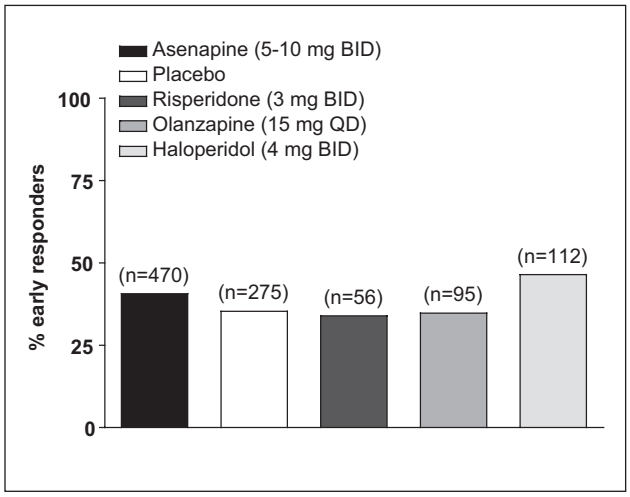


**Figure 2.** Percentage of early improvers using Positive and Negative Syndrome Scale (PANSS) assessment using a ≥20% early response cut-off value at week 2.

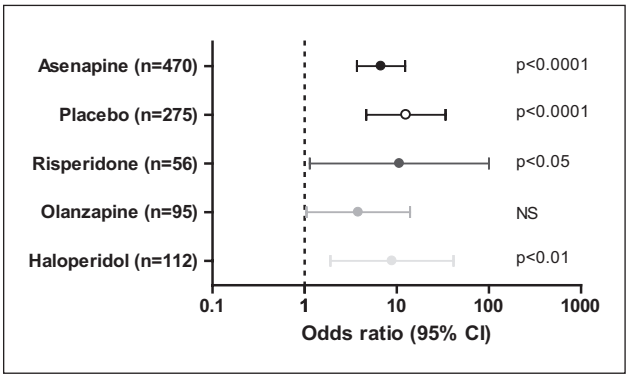


**Figure 3.** Associations between early improvement and treatment response, using Positive and Negative Syndrome Scale (PANSS) assessment; odds ratio (95% confidence interval (CI)). Early improvement defined as ≥20% reduction in PANSS total score at week 2; primary response criterion defined as a ≥50% reduction in PANSS total score at week 6; missing values considered as treatment failures. NS: non-significant.

### *Associations and predictive value of early improvement and remission using PANSS scores*

ORs were calculated to assess whether early improvement as measured by PANNS at week 2 (i.e. ≥20% reduction in total score), was associated with a higher likelihood of subsequent remission. Results showed that statistically significant associations between early improvement and remission were observed for ASE-treated patients only, as evidenced by increased ORs (ASE: 3.11, $p<0.0001$; PLA: 2.46, $p<0.05$; RIS: 0.75, $p>0.05$; OLA: 1.83, $p>0.05$; HAL: 2.35, $p>0.05$; Figure 5).

Predictive performance statistics revealed generally higher NPV rates (ASE: 82.8%, PLA: 87.1%, RIS: 67.7%, OLA: 80.8%, HAL: 76.2%), and somewhat lower PPV (ASE: 39.3%, PLA: 26.8%, RIS: 26.3%, OLA: 30.3%, HAL: 42.3%), sensitivity (ASE: 66.4%, PLA: 59.1%, RIS: 33.3%, OLA: 50.0%, HAL: 68.8%), and specificity (ASE: 61.2%, PLA: 63.0%, RIS: 60.0%, OLA: 64.6%, HAL: 51.6%) rates across treatment groups for remission (Figure 6).

## Discussion

The main findings that emerged from the analyses of three randomized controlled fixed-dose studies of ASE in patients with schizophrenia in an exacerbated state were:

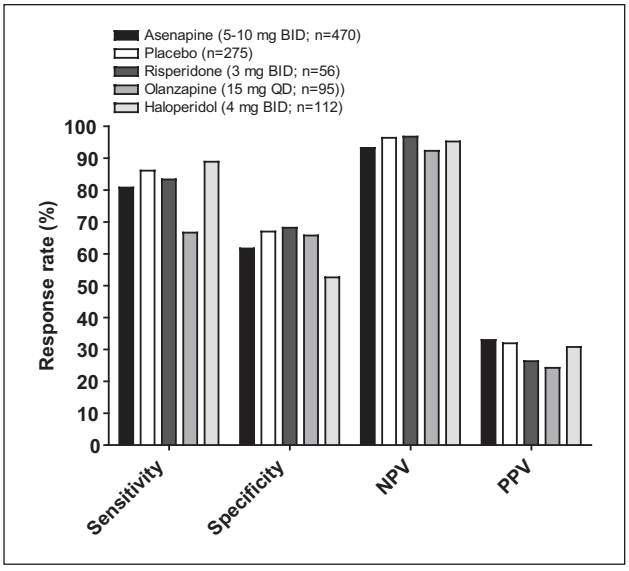


**Figure 4.** Predictive value of early improvement and treatment response using Positive and Negative Syndrome Scale (PANSS) assessment. Early improvement defined as ≥20% reduction in PANSS total score at week 2; primary response criterion defined as a ≥50% reduction in PANSS total score at week 6; missing values considered as treatment failures. NPV: negative predictive value; PPV: positive predictive value.

- Early improvement was observed in a substantial number of treated patients, using PANSS total score reduction at week 2.
- The presence of early improvement was associated with an increased OR of subsequent favorable treatment response.
- The presence of early improvement was associated with an increased OR of subsequent remission (for ASE and PLA treatment only).

Our results are in agreement with a number of other recent reports showing that early improvement at two weeks is associated with later response (Ascher-Svanum et al., 2008; Chang et al., 2006; Correll et al., 2003; Leucht et al., 2007a). However, the main advantage of the current paper, compared with some previous research using post-hoc analyses, is that we used a priori definitions to define early improvement and later response/remission. The definition of response we employed (i.e. at least 50% PANSS total score reduction), has consistently been shown to be clinically meaningful, as it reflects "much improvement" according to the CGI-S (Leucht et al., 2005b; Leucht et al., 2006; Levine et al., 2008; Schennach-Wolff et al., 2010). There is no doubt that remission is another important outcome to be considered; accordingly, we employed the standard guidelines of Andreasen et al. (2005) to define it. Our cut-off for early improvement (i.e. at least 20% PANSS total score reduction), has been shown to roughly correspond with "minimal improvement" according to CGI-S (Leucht et al., 2005b; Levine et al., 2008), and is associated with later response in a number of studies (Ascher-Svanum et al., 2008; Jager et al., 2009; Lambert et al., 2009). If early improvement is to be used as a diagnostic tool in clinical practice, a priori definitions need to be used and this is what we successfully attempted in the current paper.

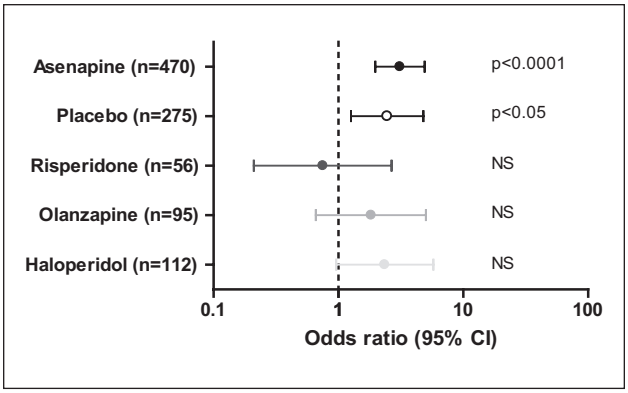


**Figure 5.** Associations between early improvement and remission using Positive and Negative Syndrome Scale (PANSS) assessment; odds ratio (OR; 95% confidence interval (CI)). Early improvement defined as ≥20% reduction in PANSS total score at week 2; remission defined as having a PANSS score of ≤3 on items P1, G9, P3, P2, G5, N1, N4 and N6 at week 6 (Andreasen et al., 2005); missing values considered as treatment failures. NS: non-significant.

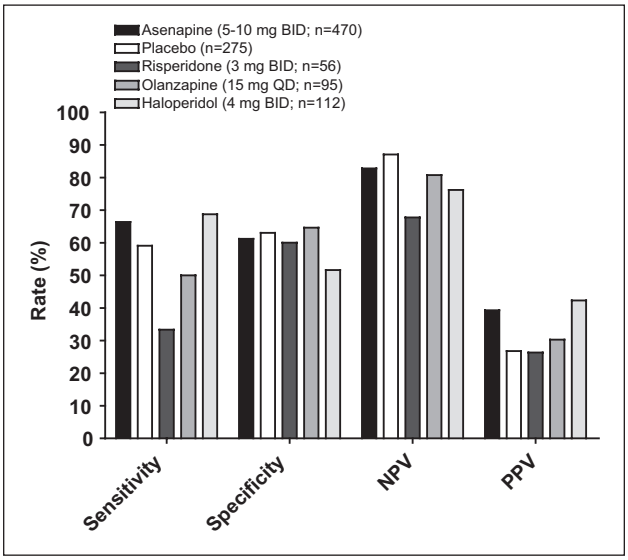


**Figure 6.** Predictive value of early improvement and remission using Positive and Negative Syndrome Scale (PANSS) assessment. Early improvement defined as ≥20% reduction in PANSS total score at week 2; remission defined as having a PANSS score of ≤3 on items P1, G9, P3, P2, G5, N1, N4 and N6 at week 6 (Andreasen et al., 2005); missing values considered as treatment failures. NPV: negative predictive value; PPV: positive predictive value.

The number of early improvers in the current analyses was relatively high. Two factors may play a part here: one is a relatively high PLA response in these trials, (i.e. 35% of the PLA-treated patients had ≥20% PANSS reduction at week 2), which most likely also empowered the response rate in the active drug-treated groups. Increasing PLA response over time has been

demonstrated (Alphs et al., 2012; Laughren, 2010), and is a major concern in current schizophrenia drug trials due to potential difficulties in separating antipsychotic drug-like effects from PLA. Another factor is that some previous trials did not subtract the minimum 30 points of the PANSS. Each of the thirty PANSS item is rated between 1 and 7, thus a PANSS total score of 30 means no symptoms. If these 30 minimum points are not subtracted for the calculation of percentage response, percentage response is underestimated (Leucht et al., 2007b, 2009a, b; Obermeier et al., 2010). If all antipsychotic drug trials had used this procedure, there would be a more optimistic impression of the effects of antipsychotic drugs for schizophrenia. For example, in a large meta-analysis comparing drugs and PLA in schizophrenia, Leucht et al., 2009a reported an overall response rate to antipsychotic drugs of 41%, which was an underestimated, because many of the individual trials had not subtracted the 30 minimum points in their calculation of percentage response. On the other hand, one could suggest, somewhat harshly, that the correction of PANSS used in the present analyses (i.e. subtraction of 30 minimum points), leads to cut-off criteria that do not necessarily correspond to those cut-off percentiles used extensively in the literature. However, correction of the PANSS gives a more realistic estimation of percentage response, not doing so underestimates response.

PLA had the numerically highest OR for the prediction of response by early improvement (12.59 for PANSS total score reduction ≥50%). This can be interpreted in the sense that if clinicians tried "no treatment" in practice, which they sometimes do to be certain about the diagnosis, they could categorically differentiate the PLA responders quite early. However, this finding could also be explained by the higher NPV. It does not necessarily mean that a patient who improves early on with PLA will eventually benefit from the drug (low PPV). Moreover, the early prediction of response was significant for the pooled analysis of ASE, RIS and PLA-treated groups. This is important in that the results are, to a certain extent, generalizable. In contrast to previous work (e.g. Ascher-Svanum et al., 2008), the results of the OLA-treated group were not significant – which may in part be explained by a lower sample size, although the ORs were also numerically higher for ASE and PLA. This observation was even more apparent in the prediction of remission, where ASE and PLA were the only significant compounds.

## Limitations

The results of the current analyses need to be considered in the light of the following limitations. While it is a major advantage that definitions for early improvement and later response/remission were chosen a priori, the analyses are still a post-hoc examination of registrational randomized ASE trials. Registrational trials have certain strengths (e.g. stringent designs, double-blind etc.), but there are also limitations (e.g. tight inclusion criteria), resulting in the generalizability of such trials to routine care being called into question as often only 10–15% of eligible patients are finally included (Hofer et al., 2000; Riedel et al., 2005). More studies under naturalistic conditions, with the a priori aim to examine the prediction of response by early improvement, are still needed. These studies might also overcome the high drop-out rates that are typical for PLA-controlled antipsychotic drug trials (Kemmler et al., 2005), and that were also a limitation of the current paper. In the published trials included in our analyses, 46% versus 34% (ASE 5 mg versus PLA, respectively; Potkin et al., 2007), and 62–67% versus 57% (ASE 5–10 mg versus PLA, respectively; Kane et al., 2010) completed the trials. We used a conservative assumption classifying drop-outs as treatment failures. High rates of discontinuation are most often due to poor therapeutic response (Liu-Seifert et al., 2005). As the trials were conducted for Food and Drug Administration registration of ASE, the sample sizes of the OLA, RIS and HAL groups were smaller, reducing precision for these drugs. Clearly, the results of the present analyses cannot be automatically generalized to other compounds, although research on amisulpride (Leucht et al., 2007a), olanzapine (Ascher-Svanum et al., 2008), RIS (Chang et al., 2006), and zotepine (Lin et al., 2007), showed similar results.

Another limitation of the current analyses is that the duration of treatment of the current episode prior to entering each clinical trial is an unknown variable which might also play an important role in determining a relationship between early response and subsequent response/remission. Very few patients enter such trials before having received some treatment for the current episode, and our data should be considered with this fact in mind.

Finally, we observed excellent sensitivity and NPV (especially for prediction of response, and somewhat less so for remission), but lower specificity and PPV. Our finding of high NPV is most important, as it shows that the chance of being a non-responder/remitter is very strong if there is no early improvement. In other words, if physicians do not see an improvement after two weeks, our data suggest that they should consider switching treatments. Although high NPV would be expected in the PLA group, the observation that early improvement on PLA was associated with increased likelihood of achieving remission is surprising, as one might assume that an early PLA response in a patient who had experienced a psychotic relapse would not be sustained and lead to remission. The present analyses did not employ the time component of the remission criteria, i.e. at least six months, but only the symptom criteria, proposed by Andreasen et al. (2005). Overall, there is currently not enough randomized evidence to demonstrate that early switching is successful. Two pilot studies by Hatta et al. (2011) were too small to show a significant effect. Kinon et al. (2010) found that switching early non-improvers from RIS to OLA was associated with significantly more improvement than keeping patients on RIS, but the effect was small. A randomized trial which examines the switch from amisulpride or OLA to the respective other drug is underway (the SWITCH study, ClinicalTrials.gov Identifier: NCT01029769).

## Conclusion

In patients suffering from schizophrenia, early improvement within two weeks of treatment was associated with increased ORs of endpoint response across treatment groups. A significant OR relationship between early improvement and remission was only observed in ASE and PLA-treated patients. It is suggested that absence of improvement within two weeks of treatment may predict the unlikely success of subsequent pharmacological intervention. Ultimately, randomized controlled trials need to demonstrate whether an early switch of the antipsychotic leads to improved outcomes.

## Conflict of interest

In the last three years Stefan Leucht has received honoraria for lectures from Abbvie, Astra Zeneca, BristolMyersSquibb, ICON, EliLilly, Janssen, Johnson & Johnson, Roche, SanofiAventis, Lundbeck and Pfizer; for consulting/advisory boards from Roche, EliLilly, Medavante, BristolMyersSquibb, Alkermes, Janssen, Johnson & Johnson and Lundbeck. EliLilly has provided medication for a study with SL als primary investigator.

J Zhao was an employee of Merck when the analyses were carried out.

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