Early prediction of clinical and functional outcome in schizophrenia

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Abstract
The objective of this paper was to investigate the prognostic and predictive value of a small panel of independent and clinically important factors based on symptom improvement, baseline cognitive impairment, and weight change during the early treatment phase. Methods: The study sample was based on a double-blind, 6-month continuation study of ziprasidone and olanzapine (N=94). We developed a parsimonious 6-month GAF prediction function using a logistic regression model, and evaluated its predictive accuracy and performance using bootstrap estimates of c-statistics and error in predicted probability. Results: At up to 6 months of follow-up, 52 (55%) of all subjects treated with ziprasidone or olanzapine met the responder criterion of \(Z\geq50\%\) improvement in GAF. At Week 2 (acute phase), the majority of ziprasidone (75%) and olanzapine (70%) patients showed greater than 25\% improvement in the BPRS psychotic symptom subscale score. These early psychotic symptom responders (Week 2) showed significantly greater improvement in global functioning than early non-responders at all time points (Week 6 and Month 6) (all \(p\)'s < 0.05), confirming early response as an indicator of continued responsiveness to treatment over at least 6 months. A multivariate prediction function based on baseline neurocognitive scores and GAF, early reduction of psychotic symptoms at 2 weeks, and percentage of weight change observed at 6 weeks (All \(p\)'s < 0.05), showed statistically acceptable predictive performance (bootstrap c-statistics=0.8598). Conclusions: Our findings suggest that a parsimonious model incorporating a psychotic symptom assessment score, baseline neurocognitive performance, and risk of weight gain can be developed for predicting patients’ likelihood of achieving favorable, long-term treatment outcomes.

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1. Introduction

Historically, treatment of schizophrenia has focused on clinical response although more recently attention has turned to the importance of functional recovery (Cassidy et al., 2010; Milev et al., 2005; Robinson et al., 2004; Stahl et al., 2010). This raises the question of how these two outcomes interface; early in treatment clinical response is routinely the central issue, but it would assist clinicians considerably if they could use this information to determine longer term functional changes.

This line of questioning dovetails with current shifts in thinking regarding time to antipsychotic response. Specifically, the once dominant delayed onset of action hypothesis that has shaped schizophrenia treatment guidelines for many years (i.e. delays of 4-8 weeks in switching antipsychotic agents to optimize chance of response), has recently been challenged (Agid et al., 2003; Kapur et al., 2005; Leucht et al., 2005). In line with earlier findings reporting rapid response to antipsychotic drug therapy (Bartko et al., 1987; Delay et al., 1952; May et al., 1980; Stern et al., 1993), proponents of the revived early response concept have demonstrated rapid antipsychotic efficacy, distinct from drug-induced non-specific effects on behavior such as agitation and excitement, within the first 24 h of treatment. In addition, this work has demonstrated that the greatest improvement in psychotic symptoms occurs during the first 2 weeks (Agid et al., 2003, 2006, 2008; Kapur et al., 2005; Leucht et al., 2005). Other corroborative studies have demonstrated that early reductions in psychotic symptoms translate to sustained improvement, thus providing a means of predicting significant, symptomatic improvement in association with long-term therapy (Kinon et al., 2008).

This said, considerable attention has now turned to functional outcome measures, a shift that reflects changing expectations regarding schizophrenia and its treatment, as well as a greater focus on recovery (Andreasen et al., 2005; Bowie et al., 2006; Cassidy et al., 2010; Milev et al., 2005; Robinson et al., 2004; Schooler, 2006; Stahl et al., 2010). Notably, although antipsychotics impact positive symptoms, their effect on cognitive, negative and other symptom domains is, at best, limited, and this holds true for both first and second generation antipsychotics (Jones et al., 2006; Schooler, 2006). Improvement in positive symptoms alone, however, has not been found to correlate significantly with functional recovery (Foussias et al., 2009; Heinrichs et al., 2009; Wittorf et al., 2008), whereas this has been demonstrated for cognitive symptoms (Bowie et al., 2006; Buchanan et al., 2005). There are limited data on association of weight gain with global functioning in schizophrenia, although a link has been reported with clinical response (Aas, 2010; Piersma and Boes, 1997; Salvi et al., 2005; Vatnaland et al., 2007; Khin et al., 2012). Of note, weight gain has been shown to be a significant predictor of poorer 12-month global functioning in bipolar 1 disorder following a first manic episode (Bond et al., 2010).

The objective of this paper was to investigate the prognostic and predictive value of early response variables (i.e. within 6 weeks) for functional outcome at 6 months in acutely ill inpatients with schizophrenia. To address this issue the GAF, a well-established and widely used instrument for assessing overall psychological, social and occupational functioning, was employed (Aas, 2010; Hall, 1995; Jones et al., 1995). We were particularly interested in assessing whether early response in psychotic symptoms predicts longer term functional outcome, an important question as this could assist clinicians in their decision-making regarding continuing or switching antipsychotic therapy. To this end, early antipsychotic response (≥ 20% improvement in BPRS psychosis subscale score) was examined for its predictive value in improved global functioning (≥ 50% gain in GAF score) over the longer term (up to 6 months). We also examined other symptom domains and tolerability markers, specifically weight gain and movement disorders.

The present study developed a simplified predictive model for 6-month GAF measure, building on the early psychotic symptom improvement factor (BPRS psychotic symptom subscale score during the first 2 weeks), baseline cognitive impairment (composite Z-score), and early tolerability measures, that is, movement disorders and metabolic risk factor (weight gain during Week 1-Week 6). We evaluated the utility and predictive accuracy of the combined early response and tolerability outcomes in global functioning prediction, using a 6-month study of ziprasidone and olanzapine. This approach emphasizes established, independent, and clinically important factors that can discriminate risk-versus-benefits of alternative treatment interventions, rather than the commonly used, data-driven stepwise variable selection method. The resultant logistic prediction model might serve as a basis for building a Framingham-like multivariate benefit-risk scoring algorithm that could extend the previous findings to a more general patient population with schizophrenia (D’Agostino et al., 2008).

2. Methods

2.1. Study subjects

This post-hoc analysis was based on a double-blind, 6-month study of ziprasidone and olanzapine in acutely ill, recently admitted inpatients with a primary psychiatric diagnosis of schizophrenia or schizoaffective disorder (N=94) (Simpson et al., 2004, 2005). Patients with primary DSM-IV axis I psychiatric disorders other than schizophrenia/schizoaffective disorder or DSM-IV-defined psychoactive substance abuse/dependence in the preceding 3 months were excluded (Simpson et al., 2004). Enrollment criteria for the 6-month continuation study included (1) completion of 6 weeks’ double-blind treatment with ziprasidone or olanzapine, (2) a CGI improvement score of ≤ 2 or a ≥ 20% reduction in Positive and Negative Syndrome Scale (PANSS) total score at acute-study endpoint, and (3) outpatient status. This study was conducted in accordance with the principles of the Helsinki Declaration and was in compliance with Good Clinical Practice. The protocol and related informed consent form were approved by the institutional review boards of the participating sites. Patients or their legal representatives provided written informed consent before any protocol-related procedures were performed. A full description of the patient sample characteristics, treatment protocols, and primary findings can be found in Simpson et al. (2004, 2005).

2.2. Treatments

All study medication was identically over-encapsulated to preserve the double-blind. In the olanzapine group, placebo capsules were employed to simulate twice-a-day dosing during the 6-month study period. Flexible dosing (ziprasidone, 40, 60, or 80 mg b.i.d;
olanzapine, 5, 10, or 15 mg/d) based on investigators’ clinical judgment, was permitted in the double-blind continuation phase. During the double-blind acute phase, subjects were randomized in a 1:1 ratio to a fixed dose of study drug for the first week of treatment (ziprasidone 40 mg twice daily on Days 1 and 2, 80 mg twice daily on Days 3-7; olanzapine 5 mg once daily on Days 1 and 2, 10 mg once daily on Days 3-7). Dosing was flexible during Weeks 2 through 6 (ziprasidone 40, 60 or 80 mg twice daily; olanzapine 5, 10 or 15 mg once daily). During weeks 3-6, subjects remained inpatients unless they met all protocol criteria for hospital discharge.

2.3. Outcome measures

Long-term functioning was based on the DSM-IV GAF scale, evaluated at the 6-month scheduled endpoint or early discontinuation visit. The GAF is well-known, highly generalizable (Pedersen et al., 2007), and has been used in many outcome studies (Aas, 2010; Piersma and Boes, 1997; Salvi et al., 2005; Vatnaland et al., 2007). In the US, the GAF is used as a national mental health outcome measure by the Department of Veterans Affairs for all patients (Greenberg and Roesnheck, 2005), while in Norway the GAF is evaluated as a part of the minimum basic dataset for all mental health services (Fallmyr and Repal, 2002). The GAF rates overall psychological, social, and occupational functioning with scores from 1 (most impaired) to 100 (least impaired). A score of zero indicates inadequate information for assessment.

2.4. Potential predictors

Predictors of GAF to be tested in the model included early psychotic symptom improvement (≥20% change in BPRS psychotic symptom subscale from baseline to Week 2) (Agid et al., 2003, 2006, 2008; Kapur et al., 2005; Leucht et al., 2005), baseline cognitive impairment (composite Z-score) (Bowie et al., 2006; Buchanan et al., 2005), total number of days experiencing movement disorders during Week 1–Week 6, and early weight change (at Week 6) (Bond et al., 2010). Baseline cognitive impairment was derived as a composite standardized score (SD=1) of cognitive tests measuring attention, motor speed, memory, executive functioning, and verbal skills at baseline. Other early response predictors, including GAF change score at Week 6, movement disorder duration (as measured by MDSB, Movement Disorder Burden Score) from baseline to Week 6 (Addington et al., 2004), and treatment assignment (ziprasidone vs. olanzapine), were also investigated.

2.5. Statistical methods

In this post-hoc analysis, the primary measure of functioning was the dichotomous GAF score based on ≥50% improvement from baseline to Month 6 endpoint. We applied a logistic regression model to build a parsimonious prediction function for the likelihood of achieving ≥50% improvement in GAF, based on the predictive performance of the pre-specified early response factors and clinical characteristics. These included early psychotic symptom improvement (≥20% change in BPRS psychotic symptom subscale from baseline to Week 2), baseline cognitive impairment (composite standardized Z-score with SD=1), number of days experiencing movement disorders during Week 1–Week 6, and weight gain at Week 6. A generalized additive model (GAM), which analyzed the percentages of GAF change score at Month 6 as nonparametric smoothed functions of the pre-specified multivariate predictors, was applied to provide graphical analysis and check for model assumptions. The performance and predictive accuracy of this multivariate prediction function were evaluated using c-statistics for discrimination and maximum absolute error in predicted probability for recalibration (D’Agostino et al., 2008). Bootstrap resampling method was used to assess the accuracy of predictions and performance statistics (Efron and Tibshirani, 1993).

3. Results

Patient characteristics of the study sample (N=94) are summarized in Table 1. Both ziprasidone and olanzapine groups were comparable in age, gender distribution, body weight, and baseline clinical characteristics. The median average daily doses for olanzapine and ziprasidone were 15 mg/d and 151 mg/d, respectively. There were no statistically significant differences between the olanzapine and ziprasidone groups in GAF at all time points after week 6 (t=0.9986, p=0.3215, LOCF) or month 6 (t=1.5816, p=0.1172, LOCF). Treatment, therefore, was not included as a predictor for the 6-month GAF model.

3.1. Early psychotic response

Table 1  Summary of patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Olanzapine Mean (95% CI)</th>
<th>Ziprasidone Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Mean (SD)</td>
<td>36 (10)</td>
<td>38 (10)</td>
</tr>
<tr>
<td>Gender, % Male</td>
<td>76%</td>
<td>60%</td>
</tr>
<tr>
<td>Baseline body weight, Mean (SD)</td>
<td>84 (20)</td>
<td>84 (21)</td>
</tr>
<tr>
<td>BPRS psychotic symptom subscale at Week 2</td>
<td>15.4 (14.5, 16.2)</td>
<td>15.9 (14.6, 17.2)</td>
</tr>
<tr>
<td>BPRS psychotic symptom subscale change score at Week 6</td>
<td>-5.3 (−6.2, −4.4)</td>
<td>-5.5 (−6.8, −4.1)</td>
</tr>
<tr>
<td>BPRS total score</td>
<td>51.2 (47.8, 54.4)</td>
<td>51.9 (48.6, 55.2)</td>
</tr>
<tr>
<td>GAF change score at Week 6</td>
<td>22.6 (18.3, 26.9)</td>
<td>21.0 (15.7, 26.4)</td>
</tr>
<tr>
<td>GAF change score at Month 6</td>
<td>16.8 (12.4, 21.2)</td>
<td>22.6 (17.0, 28.2)</td>
</tr>
</tbody>
</table>

***p < 0.05.
improvement in BPRS psychotic symptom scores. At up to 6 months of follow-up, 52 (55%) of all subjects on either treatment met the global functioning criterion of ≥50% improvement in GAF. Early responders who achieved ≥20% improvement in BPRS psychotic symptom subscale scores at Week 2 showed significantly greater improvement in GAF than early non-responders at all subsequent time points after week 6 (p<0.01, t=2.694) or month 6 (p=0.020, t=2.369) (Figure 2). Percentage improvement in BPRS psychotic symptom subscale score at Week 2 predicted subsequent GAF improvement at Month 6 (p<0.05, t=−1.96) (Table 2, Figure 3).

3.2. Baseline neurocognitive improvement at randomization

Global cognitive composite standardized Z-score with SD=1 was derived by averaging the standardized score (SD=1) on each of the contributing domain tests: attention (continuous performance test, trail-making test Part A), memory (verbal memory), digit span distraction test, and executive functions (Wisconsin card sorting test, trail-making test Part B, verbal fluency test). The derived global cognitive composite standardized Z-score was examined for normality of distribution and potential ceiling/floor effects (Figure 4a). Patients with higher cognitive impairment at baseline were associated with more severe BPRS psychotic symptoms at baseline (p=0.036, t=−2.132) and showed greater mean GAF improvement at Month 6 (p=0.038, t=−2.101) (Figure 4b).

3.3. Early weight gain at Week 6

Subjects with clinically significant weight gain (CSWG, i.e. ≥7% weight gain) at Week 6 demonstrated significantly less GAF improvement subsequently (p=0.031, t=2.156) (Figure 5, left panel).
Among subjects with CSWG, mean weight gain at Week 6 was lower in completers compared to those who dropped out prior to Month 6 endpoint ($p=0.002$, $t=3.38$) (Figure 5, right panel).

### 3.4. Other predictor variables

GAF score at baseline ($p<0.001$) (Table 2) was a significant predictor of subsequent GAF improvement at Month 6. Gender ($p=0.06$), GAF change score at Week 6 ($P>0.11$), movement disorder duration (from baseline to Week 6) ($P>0.23$), and treatment (ziprasidone vs. olanzapine) ($p=0.92$) were non-significant predictors of subsequent GAF improvement at Month 6.

### 3.5. Prediction model validation

At up to 6 months of follow-up, 52 (55%) of all subjects from both the ziprasidone and olanzapine treatment arms met the criterion of $\geq 50\%$ improvement in GAF. Table 2 shows the multivariate logistic regression model building on the 4 pre-specified predictors of Month 6 GAF improvement ($\geq 50\%$). The proposed 4-variable score function has acceptable calibration performance based on absolute error in predicted probability (0.0575 from bootstrap resampling 200 times), and high predictive accuracy ($c$-statistics=0.85, 95% CI 0.77, 0.93; bootstrap estimate 0.8598) (Figure 6). The 10-fold cross-validated $c$-statistics for this 4-variable prediction function was 0.8413, indicating high predictive performance with great stability in model validation.

### Table 2  Multivariate logistic prediction function of Month 6 GAF ($N=94$).

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Coefficient</th>
<th>SE</th>
<th>$t$-Statistics</th>
<th>$P$-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early psychotic response</td>
<td>-3.14</td>
<td>1.60</td>
<td>-1.96</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>%BPRS score at Week 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment adherence and/or metabolic risk factor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Weight change</td>
<td>8.60</td>
<td>3.70</td>
<td>2.32</td>
<td>0.02</td>
</tr>
<tr>
<td>% Weight change $\geq 7%$</td>
<td>-12.59</td>
<td>4.53</td>
<td>-2.78</td>
<td>0.005</td>
</tr>
<tr>
<td>Baseline cognitive impairment</td>
<td>-1.85</td>
<td>0.86</td>
<td>-2.14</td>
<td>0.03</td>
</tr>
<tr>
<td>Composite standardized score (SD=1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline demographics and characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline GAF</td>
<td>-0.19</td>
<td>0.046</td>
<td>-4.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treatment (olanzapine vs. ziprasidone)</td>
<td>-0.30</td>
<td>0.60</td>
<td>-0.51</td>
<td>0.61</td>
</tr>
<tr>
<td>$c$-Statistics (AUC ROC)</td>
<td>0.85</td>
<td>95% CI (0.77, 0.93)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Age ($p=0.21$) and gender (0.35) are NS.
Adding gender to the model gave 0.8564. The average c-statistics was 0.86 from 200 bootstrap samples before adding gender to the model and 0.87 after gender was added.

4. Discussion

Our study extends existing evidence that early antipsychotic efficacy predicts clinical improvement over the longer term, demonstrating in this case that such a measure can also predict functional improvement. More specifically, early antipsychotic response (as assessed by ≥20% improvement in the BPRS psychotic symptom subscale at Week 2) in acutely ill inpatients predicted subsequent improvement in global functioning (≥50% improvement in GAF) for up to 6 months with high predictive performance and accuracy. This has important treatment implications. It is common practice for antipsychotic trials to be extended for weeks or even months in an effort to achieve response, a strategy that has been incorporated in more recent trials such as CATIE (Lieberman et al., 2005). Indeed, this could at least in part contribute to the large number of trial subjects who dropped out for lack of efficacy or intolerance; overall, 74% of patients in CATIE discontinued their assigned treatment before the 18-month endpoint, raising issues as to whether this is the best strategy to differentiate antipsychotic treatments (Murphy et al., 2006). A more appropriate approach to assessing antipsychotic effect may perhaps be testing patients for early drug response, adapting or...
switching medication according to demonstrated efficacy and tolerability, then following the adjusted regimen to monitor for long-term treatment adherence and outcome (Stahl et al., 2010).

The present study also highlights the relationship between the risk of adverse effects early in antipsychotic treatment and future functioning. Long-term GAF improvement was found to be inversely associated with early weight gain (≥7% at Week 6 compared to baseline; \( p < 0.05 \)), a finding at odds with earlier studies reporting a significant association between drug-induced weight gain and clinical symptom reduction with clozapine (Meltzer et al., 2003) or olanzapine (Ascher-Svanum et al., 2005; Basson et al., 2001) treatments. On the other hand, our finding is consistent with a recent review by the US Food and Drug Administration (32 registration trials of 4- to 8-wk duration, conducted from 1991 to 2009 in 11,567 patients) which showed treatment effects decreased with increase of body weight,

Figure 5  Week-6 weight gain (%): predictor of GAF change (%) and dropout at Month 6 (\( N = 94 \)).

Figure 6  Multivariate prediction function for long-term global functioning. Logistic prediction model for GAF (≥50% improvement at Month-6 included terms for early psychotic response (%) at Week-2, weight gain (%) at Week-6, cognitive composite Z-score at baseline, and baseline GAF.
especially in North American trials (Khin et al., 2012). Previous reports suggest that the efficacy of ziprasidone (Allison et al., 1999; Lieberman et al., 2003; Leucht et al., 2009; aripiprazole (Potkin et al., 2003; Leucht et al., 2009; Rummel-klug et al., 2010), and lurasidone (Meltzer et al., 2011) have not been associated with significant weight gain, since these drugs are situated at significantly lower end of the drug-induced weight gain spectrum. The present findings are particularly relevant in light of the marked liability for weight gain associated with second generation antipsychotics as a class.

Baseline neurocognitive impairment, as assessed by the global composite Z-score, was associated with higher level of baseline symptom severity in the acutely ill inpatients enrolled in the initial phase of this study. We found higher baseline neurocognitive impairment was predictive of greater improvement in global functioning at Month 6 ($p<0.05$), at odds with evidence underscoring a link between cognitive deficits and functional impairment (Addington et al., 1991; Bowie et al., 2006; Bowie and Harvey, 2006; Leifker et al., 2009; Milev et al., 2005). It is possible that the observed inverse relationship noted here was influenced by the level of psychotic symptom severity at baseline. Alternatively, it has been shown that in individuals with schizophrenia higher cognitive performance at baseline is also associated with lower medication adherence and poorer clinical outcome (Perkins et al., 2008). That cognition and functional outcome are interrelated appears clear (Addington et al., 1991; Bowie et al., 2006; Bowie and Harvey, 2006; Leifker et al., 2009; Milev et al., 2005); what is less clear, however, is the exact nature of this relationship and the impact of the measures we employ to define each.

In summary, our study demonstrates that a composite of early response/side effect measures can predict continued response and favorable, long-term functional improvement. Nonetheless, this post-hoc analysis is preliminary and has its own limitations. Its sample size is small, and findings need to be replicated independently in larger studies and datasets. Whether it is more reliable to measure a patient’s neurocognitive impairment at baseline, or when the patient’s psychiatric condition has stabilized needs to be assessed. It is not clear whether other adverse events besides weight change (e.g. sedation) may also be significant predictors of long-term treatment outcome and functioning. Findings of this study must therefore be considered exploratory; however, the results argue strongly for further investigations of this sort. Expectations regarding outcome in schizophrenia have expanded, and clinical practice would benefit considerably from any strategy allowing clinicians to predict both symptomatic and functional outcome early in the course of treatment (Davidson and Keefe, 1995; Sevy and Davidson, 1995).

Role of the funding source

The sponsor was involved in the design, conduct, and analysis of the clinical trial reported in this paper. Data analysis was supported by Data Power (DP), Inc., and interpreted collectively by all of the authors.

Contributors

Dr. Siu wrote the first draft of the paper with Drs. Agid and Remington. Statistical analysis was performed by Dr. Siu. All authors contributed to subsequent revisions critically for important intellectual content, and to approval of the final version for publication.

Conflict of interest

Ofer Agid has received grant support, funding, or has been a paid consultant to the following companies that conducted scientific or medical research and/or marketed medications related to psychiatric disorders: Janssen-Ortho (Johnson & Johnson); Eli Lilly Inc., US; Eli Lilly Canada; Novartis; Sepracor Inc., US; Sunovion US. Cynthia Siu was a paid consultant to Pfizer and has served as a consultant to Pfizer, Dainippon Sumitomo Pharma America/Sunovion, and Wyeth/Pfizer over the past 3 years. Gary Remington has received research support (Principal Investigator) from the following funding agencies: Canadian Institutes of Health Research, Schizophrenia Society of Ontario, and the Canadian Diabetes Association. As a Principal Investigator, he has also received support from Novartis Canada, Medicure Inc., and Neurocrine Bioscience. He has received consultant fees from CanAm Bioresearch Inc., Laboratorios Farmaceuticos ROVI, and speaker’s fees from Novartis. He holds no commercial investments in any pharmaceutical company. Elizabeth Pappadopulos and Douglas Vanderburg are full time employees of Pfizer Inc.

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