Impact of DSM-5 Changes on the Diagnosis and Acute Treatment of Schizophrenia

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Objective: To examine the consequences and validity of changes in Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 diagnostic criteria for schizophrenia, eg, omission of subtypes, using a large dataset of double-blind, randomized, placebo-controlled schizophrenia trials. Methods: Data from 22 short-term efficacy registration trials of second generation antipsychotics for the treatment of acute psychotic episodes in patients with schizophrenia (N = 5233), submitted to the Dutch regulatory authority were analyzed. We examined whether patients in these pre-DSM-5 trials met the diagnostic criteria for schizophrenia according to DSM-5. Using linear regression, we examined differences in effect size between DSM-IV subtypes and between DSM-5 symptom dimensions. Results: Over 99.5% of the patients met DSM-5 diagnostic criteria for schizophrenia and no differences in effect size were found between schizophrenia subtypes (P = .65). Symptom dimensions that respond best to treatment with second generation antipsychotics were hallucinations, delusions, disorganized speech, and mania (Hedge’s g = −0.23 to −0.31). Conclusions: Results of clinical trials in patients with pre-DSM-5 schizophrenia also apply to patients diagnosed with DSM-5 schizophrenia. Omission of the classic subtypes is justified as they are not predictive of response to treatment. The DSM-5 C-RDPSS scale adds valuable information to the categorical diagnosis of schizophrenia, which is relevant for antipsychotic response.

Key words: antipsychotics/clinical trials-diagnostic criteria

Introduction

Schizophrenia is characterized by positive symptoms (eg hallucinations), negative symptoms (eg flat affect), and impairments in cognition (eg attention). Patient’s social and occupational functioning are commonly severely affected. Life-time prevalence of schizophrenia is estimated at 0.7%.1

Schizophrenia is diagnosed with criteria laid down in the Diagnostic and Statistical Manual of Mental Disorders (DSM).2 In 2013, the fifth edition of the DSM (DSM-5) became available with some important changes concerning schizophrenia. These include changes in diagnostic criteria, omission of the schizophrenia subtypes, and addition of a new scale to assess the severity of symptom dimensions (C-RDPSS).

Changes in the Diagnostic Criteria

In contrast to DSM-IV, in DSM-5 a patient is always required to have at least 2 characteristic symptoms. Thus, the special position of bizarre delusions or Schneider first-rank auditory hallucinations has been omitted, due to the nonspecificity of the Schneider first-rank symptoms3–6 and the unreliability of the distinction between bizarre and nonbizarre delusions.7–9 Several trials have also demonstrated that the number of patients diagnosed with schizophrenia based on the presence of only bizarre delusions or first-rank auditory hallucinations is low.10–13

In addition, in DSM-5, a patient is required to have at least one of the following positive symptoms: delusions, hallucinations, or disorganized speech.

Omission of Schizophrenia Subtypes

The rationale for omitting the subtypes of schizophrenia in DSM-5 is that the subtypes did not adequately reflect the heterogeneity of schizophrenia. Moreover, subtype stability over time was low and only some of the subtypes were used clinically.14 no differences in sociodemographic or cognitive characteristics have been found
between subtypes,\textsuperscript{15} they do not predict the course of the illness,\textsuperscript{13} and in several cluster analyses, patients could not be assigned to a subtype based on their symptoms.\textsuperscript{16–19} Finally, scientific reports do not use subtyping anymore.\textsuperscript{20} Examining differences in the response to treatment by subtype is relevant for the validity of the omission of subtypes in DSM-5.\textsuperscript{21}

**Addition of a Scale to Assess the Severity of Symptom Dimensions (C-RDPSS)**

With the omission of subtypes in DSM-5, the characterization of patients has shifted to symptom dimensions, including reality distortion (delusions, hallucinations), negative symptoms, disorganization, cognitive impairment, motor symptoms (eg catatonia), and mood symptoms (depression, mania). These symptom dimensions have distinctive courses, patterns of treatment response, and prognostic implications. The severity of the symptom dimensions varies from patient to patient and within a patient during the course of the illness. Through assessing the severity of these dimensions, the clinician can attain a picture of the nature of the disorder in a particular patient and assess the impact of treatment on different aspects of patient’s illness. For this purpose, the DSM-5 has introduced a new scale, the Clinician-Rated Dimensions of Psychosis Symptom Severity (C-RDPSS). The scale is presented in the supplementary table S1. The development of the scale and justification for introducing it in DSM-5 is discussed by Tandon et al.\textsuperscript{22} Some criticism has been directed to this scale, eg with respect to the annotations defining the dimensions, the assessment of cognition, and the overall reliability and validity of the scale.\textsuperscript{23–25}

This study aims to empirically test the consequences and validity of the 3 important changes for schizophrenia from DSM-IV to DSM-5, using a large dataset (\(N = 5233\)) of randomized, placebo-controlled trials of second generation antipsychotics (SGAs). First, we examine whether patients included in these pre-DSM-5 trials also met DSM-5 criteria. The individual items on the Brief Psychiatric Rating Scale\textsuperscript{26} (BPRS) were assigned to the corresponding criterion \(A\) symptoms. We checked whether patients met at least 2 criteria and whether they had at least one of the specific positive symptoms (delusions, hallucinations, or disorganized speech) according to the BPRS items.

**Analysis of DSM-5 Criteria**

We examined whether patients included in these pre-DSM-5 trials also met DSM-5 criteria. The individual items on the Brief Psychiatric Rating Scale\textsuperscript{26} (BPRS) were assigned to the corresponding criterion \(A\) symptoms. We checked whether patients met at least 2 criteria and whether they had at least one of the specific positive symptoms (delusions, hallucinations, or disorganized speech) according to the BPRS items.

**Analysis of Schizophrenia Subtypes**

We examined differences in treatment effect across schizophrenia subtypes. Information on DSM-IV subtypes was recorded in the raw dataset and was based on clinical judgement of the study clinician. The \(1–7\) scale of the BPRS was the main efficacy parameter chosen for the comparison between subtypes, analyzed for mean change from baseline. If no BPRS data were available, data from the Positive and Negative Symptom Scale\textsuperscript{27} (PANSS) were converted to BPRS scores. For any missing data on individual item scores on the PANSS scale, the average of the other PANSS item scores for the particular patient for that visit was used. The 6 weeks measurement was chosen for the primary endpoint, according to recommendation of the European Medicines Agency (EMA) guideline on schizophrenia trials\textsuperscript{28} (EMA/CHMP/40072/2010 Rev.1). For trials with a shorter duration than 6 weeks or for patients who dropped out before the end of a 6-week study, the last observation was carried forward to week 6.

All patients with at least 1 postbaseline assessment were included in the analysis. Active comparator arms and treatment arms with dosages lower than the dose indicated in the Summary of Product Characteristics (SPC) of each compound were excluded from the analysis. This was done to avoid bias due to ineffective doses in some of the trials.

Linear mixed model regression analysis with change in BPRS score as dependent variable and treatment condition, subtype and the treatment condition by subtype interaction was used to examine whether subtype modified the effect of treatment. In this analysis, study was used as a level 2 variable. A random intercept was used to account for dependencies within trials. The used software was IBM SPSS Statistics version 20.

**Analysis on C-RDPSS**

In order to obtain a proxy for the C-RDPSS scores, 4 independent psychiatrists blindly assigned the best corresponding BPRS items to the C-RDPSS dimension. The consensus of this conversion is presented in supplementary table S2. In cases where 2 BPRS items were assigned by the psychiatrist to 1 C-RDPSS item, the highest BPRS score was chosen as the best corresponding C-RDPSS score.

To compare the effects on several symptom dimensions, Hedge’s \(g\) was calculated as an adjusted standardized
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**Result**

**Trials**

Of the total 29 trials that were requested, 22 (76%) were submitted, including data from 5233 patients. The trials examined efficacy of 5 different SGAs.

**Analysis of DSM-5 Criteria**

All patients except 1 had at least 2 criteria A symptoms (>99.9%) and 22 patients (0.4% of the total population) did not have any of the required 3 positive symptoms. Altogether, the vast majority (>99.5%) of patients with schizophrenia in these pre DSM-5 trials would have met DSM-5 criteria for schizophrenia.

**Analysis of Schizophrenia Subtypes**

Information regarding schizophrenia subtypes was available in 19 of the trials, performed with 4 different SGAs. Table 1 presents patient characteristics of this dataset. As only few patients were of the catatonic or residual subtype, these patients were excluded from further analysis. Table 1 shows that there were only small differences in patient characteristics between the disorganized, paranoid, and undifferentiated patients in terms of age, sex, and BPRS baseline score.

Table 1 also presents the mean change in BPRS total score from baseline to week 6 by schizophrenia subtype. Linear regression analysis suggest that the differences between the subtypes are not statistically significant ($P = .65$).

**Analysis on C-RDPSS**

Table 2 presents the adjusted standardized mean difference in C-RDPSS scores between placebo and active treatment at baseline and at week 6. Figure 1 presents these results graphically. As expected in a randomized trial, the mean C-RDPSS scores at baseline are very similar for both treatment conditions. Figure 1 suggests that the dimensions that respond the best to treatment with SGAs are hallucinations, delusions, disorganized speech, and mania, with Hedge's g values ranging from −0.23 to −0.31. Abnormal psychomotor behavior, negative symptoms, depression, and cognitive impairment show little improvement, with Hedge's g ranging between −0.15 and −0.18. However, the differences in improvement between all dimension scores are still relatively small.

Table 3 presents the standardized mean difference in C-RDPSS scores between BPRS responders and nonresponders at baseline and at week 6. Figure 2 presents these results graphically. Overall, 31% of the patients in the active arms and 19% in the placebo group were responders. BPRS responders show moderate to large

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**Table 1. Patient Characteristics in the Dataset and Mean Change in BPRS Total Score From Baseline to 6 weeks by Schizophrenia Subtype**

<table>
<thead>
<tr>
<th>Schizophrenia subtype</th>
<th>Patients active/ placebo $N$</th>
<th>Age mean (SD)</th>
<th>Sex (% male)</th>
<th>Ethnicity</th>
<th>BPRS baseline score mean (SD)</th>
<th>Change from baseline in total BPRS score (SD)</th>
<th>Ratio active vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disorganized</td>
<td>134/60</td>
<td>35.4 (10.5)</td>
<td>73.7%</td>
<td>Caucasian Black 59.8% 21.1% Other 19.1%</td>
<td>57.3 (11.0)</td>
<td>$-4.3$ (14.0)</td>
<td>$-10.0$ (12.9)</td>
</tr>
<tr>
<td>Catatonic</td>
<td>17/5</td>
<td>34.5 (13.5)</td>
<td>68.2%</td>
<td>Caucasian Black 77.3% 9.1% Other 13.6%</td>
<td>58.8 (13.4)</td>
<td>N.A</td>
<td>N.A</td>
</tr>
<tr>
<td>Paranoid</td>
<td>2308/901</td>
<td>39.4 (11.6)</td>
<td>68.7%</td>
<td>Caucasian Black 62.8% 25.5% Other 11.7%</td>
<td>53.7 (9.1)</td>
<td>$-2.9$ (16.2)</td>
<td>$-8.8$ (14.8)</td>
</tr>
<tr>
<td>Residual</td>
<td>23/16</td>
<td>42.5 (9.1)</td>
<td>92.3%</td>
<td>Caucasian Black 69.2% 15.4% Other 15.4%</td>
<td>53.1 (8.3)</td>
<td>N.A</td>
<td>N.A</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>694/305</td>
<td>32.8 (7.4)</td>
<td>74.5%</td>
<td>Caucasian Black 52.9% 26.9% Other 20.2%</td>
<td>55.1 (10.4)</td>
<td>$-1.6$ (12.7)</td>
<td>$-8.4$ (13.5)</td>
</tr>
<tr>
<td>Total</td>
<td>3176/1287</td>
<td>38.7 (11.3)</td>
<td>70.5%</td>
<td>Caucasian Black 60.5% 25.5% Other 14.0%</td>
<td>54.2 (9.6)</td>
<td>N.A</td>
<td>N.A</td>
</tr>
</tbody>
</table>
improvements in all symptom dimensions, including negative symptoms, cognition, and depression.

Discussion

The aim of this study was to examine the validity of the changes in diagnosis of schizophrenia from DSM-IV to DSM-5, ie changes in the diagnostic criteria, removal of the DSM-IV schizophrenia subtypes, and the introduction of the C-RDPSS scale.

Although patients included in our analysis were diagnosed according to older versions of the DSM, our data convincingly show that the vast majority of patients (99.5%) would also meet criteria of schizophrenia according to DSM-5. This results corroborates those of a much smaller recent study, which included 221 patients, showing that less than 2% of patients with DSM-IV schizophrenia would not meet diagnostic criteria for DSM-5 schizophrenia. Together these findings suggest that results of clinical trials in patients with pre-DSM-5 schizophrenia are valid for patients diagnosed with DSM-5 schizophrenia.

Previous studies have suggested that DSM-IV subtypes poorly reflect the heterogeneity of schizophrenia, and do not predict the course of illness, but the association between diagnostic subtypes and response to treatment has not been previously investigated. The current study shows that the effect of SGAs do not differ between DSM-IV schizophrenia subtypes, thus providing empirical support for the decision to remove the subtypes in DSM-5. Our analysis, however, included only the subtypes paranoid, disorganized, and undifferentiated. The low number of patients with residual or catatonic subtype in our sample was to be expected as all patients were included in efficacy trials of antipsychotic medication and there is consensus that catatonic patients should be treated in the acute phase with benzodiazepines and/or electroconvulsive therapy rather than antipsychotics. Catatonia is also often missed by clinicians and the clarified diagnostic criteria in DSM-5 may facilitate correct diagnosis and subsequent treatment. Moreover it is questionable whether patients with the residual subtype can benefit from antipsychotic medication.

This study further shows slightly larger effects of SGAs on the C-RDPSS symptom dimensions hallucinations, delusions and disorganized speech than on the other symptom dimensions. Although the effect on all symptom dimensions is rather small (Hedge's g ≤ −0.31), the 95%
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Confidence intervals show that for the dimensions negative symptoms, impaired cognition and depression, effect sizes vary from small (highest −0.29) to nonexistent (lowest −0.09) whereas the 95% confidence intervals for the dimensions hallucinations, delusions, and disorganized speech vary from small (lowest −0.23) to moderate (highest −0.37). Taking into account that hallucinations, delusions, and disorganized speech are core symptoms of psychosis, it was to be expected that these symptoms respond well to treatment with antipsychotics. It should be noted however, that baseline scores of cognitive impairment were very low, leaving very little space for improvement (floor effect). Furthermore, negative symptom improvement should be assessed preferably in trials specifically designed to assess these symptoms. BPRS responders showed improvement in all symptom dimensions, including negative symptoms. These findings suggest that the DSM-5 C-RDPSS scale adds valuable information, relevant for antipsychotic response, to the categorical diagnosis of schizophrenia.

This study has both several strengths and limitations. The most important strength is the large sample size and the randomized, placebo-controlled design of the included trials. A limitation of our study is that we had to convert the BPRS scale to the C-RDPSS scale. However, the descriptions of the individual items of the scales are very similar and conversion by 4 independent psychiatrists showed high consistency in assigning the corresponding items. It was difficult to find a match for the C-RDPSS item “Impaired cognition” because the BPRS does not include an item that adequately covers the cognition deficits in schizophrenia. As a best possible proxy we therefore used the BPRS item “Disorientation.” However, our results showed that the baseline scores on this BPRS item were very low with little variability and antipsychotic treatment had no effect on this symptom. Therefore, we can only conclude that the presence of a separate item for impaired cognition in the C-RDPSS might be a useful addition to existing instruments that seem to neglect this important psychopathological domain. Future research is needed to test whether this item of the C-RDPSS is the best choice.

Another limitation is that by using the BPRS as a proxy for the C-RDPSS, BPRS items were involved both in the predictor and the outcome measure in the responders vs nonresponder analysis. Our results are based on a rather specific clinical trial population in the acute treatment phase. Therefore, the results can not be directly applied to other populations.

### Table 3. Mean C-RDPSS Scores and Adjusted Standardized Mean Difference (Hedge’s g) in C-RDPSS Scores Between Nonresponders and Responders at Baseline and at Week 6

<table>
<thead>
<tr>
<th>Item</th>
<th>Non-responder (N = 3788)</th>
<th>Responder (N = 1445)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>6 weeks</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hedge’s g</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Hallucinations</th>
<th>Delusions</th>
<th>Disorganized speech</th>
<th>Abnormal psychomotor behavior</th>
<th>Negative symptoms</th>
<th>Impaired cognition</th>
<th>Depression</th>
<th>Mania</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-responder</td>
<td>2.54 (1.12)</td>
<td>3.05 (0.65)</td>
<td>2.52 (0.99)</td>
<td>1.90 (1.07)</td>
<td>2.64 (0.84)</td>
<td>1.01 (1.09)</td>
<td>1.60 (1.19)</td>
<td>2.01 (1.15)</td>
</tr>
<tr>
<td>Responders</td>
<td>2.65 (1.06)</td>
<td>3.06 (0.61)</td>
<td>2.41 (1.03)</td>
<td>1.89 (1.11)</td>
<td>2.71 (0.78)</td>
<td>0.84 (1.04)</td>
<td>1.76 (1.21)</td>
<td>2.04 (1.11)</td>
</tr>
<tr>
<td>P</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hedge’s g</td>
<td>0.09</td>
<td>0.03</td>
<td>0.03</td>
<td>-0.10</td>
<td>0.01</td>
<td>-0.15</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.03 to 0.16</td>
<td>-0.03 to 0.09</td>
<td>-0.16 to 0.04</td>
<td>-0.07 to 0.05</td>
<td>0.02 to 0.14</td>
<td>-0.21 to -0.09</td>
<td>0.07 to 0.19</td>
<td>-0.04 to 0.08</td>
</tr>
<tr>
<td>Hedge’s g 6 weeks</td>
<td>-1.23</td>
<td>-1.56</td>
<td>-1.25</td>
<td>-0.87</td>
<td>-1.06</td>
<td>-0.66</td>
<td>-0.75</td>
<td>-1.11</td>
</tr>
<tr>
<td>95% CI</td>
<td>-1.30 to -1.17</td>
<td>-1.63 to 1.49</td>
<td>-1.31 to -1.12</td>
<td>-0.93 to -0.81</td>
<td>-1.02 to -0.72</td>
<td>-0.60</td>
<td>-0.81 to -1.17</td>
<td>-0.67 to -1.04</td>
</tr>
</tbody>
</table>

Hedge’s g was calculated with the formula \( 1 - \frac{3}{4df - 1} \times \left( \frac{R_1 - R_2}{S_{\text{within}}} \right) \) where \( S_{\text{within}} = \sqrt{\frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2 - 2}} \).
extrapolated to the general patient population or to long-term effects of antipsychotics in this population.

Unfortunately we could not address the other important change in the DSM section concerning psychotic disorders, i.e. the requirement that a major mood episode has to be present for the majority of the total duration of the disorder in order to make a diagnosis of schizoaffective disorder. The inclusion criteria in the trials in our dataset required patients to be diagnosed solely with schizophrenia. Finally, our study analyses responses of patients with (different subtypes of) schizophrenia to some of the currently available antipsychotics, all of which target the dopamine system. Trials with medications targeting other systems (e.g. glutamate) could lead to other conclusions. However, currently there are very few data available regarding effective treatments directed at other neurotransmitter systems and therefore, our data represent the best available pharmacological data to date to (partially) validate the diagnostic changes from DSM-IV to DSM-5.

In conclusion, our analyses of about 5000 patients diagnosed according to pre-DSM-5 criteria for schizophrenia provide empirical support for the validity of the changes in the section concerning schizophrenia in DSM-5. Results from clinical trials in patients with a pre-DSM-5 diagnosis of schizophrenia are also valid for patients with DSM-5 schizophrenia. DSM-IV subtypes are not related to treatment response to SGAs. The C-RDPSS provides clinically useful information in patients with schizophrenia treated with SGAs. The differences in response for different symptom dimensions raises the question whether antipsychotic treatments should be specifically targeted to patients with certain symptom patterns and whether more symptom specific psychopharmacological agents are needed in the treatment of schizophrenia. Our analysis on responders does not support these suggestions, because all symptom dimensions improved in patients defined as responders.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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References


