Schizophrenia Research 150 (2013) 334–338

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Negative symptoms in schizophrenia – the remarkable impact of inclusion definitions in clinical trials and their consequences

Jonathan Rabinowitz [a,*], Nomi Werbeloff [a], Ivo Caers [b], Francine S. Mandel [c], Virginia Stauffer [d], François Menard [e], Bruce J. Kinon [d], Shitij Kapur [f]

[a] Bar Ilan University, Ramat Gan, Israel
[b] Janssen Research & Development, Beerse, Belgium
[c] Pfizer, 235 East 42nd Street, New York, NY, 10017, USA
[d] Eli Lilly, 893 South Delaware Street, Indianapolis, IN 46285, USA
[e] Lundbeck SAS, 37–45, Quai du Président Roosevelt, 92445, Paris, France
[f] Institute of Psychiatry, Kings College, London De Crespigny Park, London, SE5 8AF, UK

ARTICLE INFO

Article history:
Received 18 April 2013
Received in revised form 30 May 2013
Accepted 3 June 2013
Available online 29 June 2013

Keywords:
Negative symptoms
Antipsychotic trials

ABSTRACT

Background: Negative symptoms are an important target for intervention in schizophrenia. There is lack of clarity in defining appropriate patients for negative symptom trials. While regulators, drug developers and academics have expressed positions in this regard, the implications of these definitions are not yet tested in large-scale trials and there is no consensus.
Objectives: We examined the extent to which various operational criteria for inclusion in negative symptoms in schizophrenia clinical trials can impact patient selection and examined the effectiveness of second generation antipsychotics (SGAs) in patients with various degrees of negative symptoms.
Method: Using anonymized patient data from AstraZeneca, Janssen Pharmaceuticals, Eli Lilly, Lundbeck, and Pfizer from 20 placebo-controlled trials of SGAs in schizophrenia from the NewMeds repository, we applied different criteria for negative symptoms: *prominent, predominant*, and EMA criteria, which require predominant and core negative symptoms to be present and examined the impact of these on inclusion and outcome.
Results: Operational criteria for negative symptoms in trials vary greatly in their inclusion of patients from "typical" trial samples. Of the patients in our studies, 8.1% and 62.3% met criteria for prominent negative symptoms, 10.2% to 50.2% met criteria for predominant negative symptoms and 7.6% to 40.0% met EMA criteria at baseline. After 6 weeks of active treatment, 8% and 33.1% of patients met criteria for prominent residual negative symptoms and 14.9% to 65% met criteria for prominent and 12.2% to 45.5% met EMA criteria. Patients with predominant or prominent negative symptoms showed marked improvement on second generation antipsychotics.
Conclusions: Applying various operational criteria for selecting patients for negative symptoms trials provides a great variability in percentage of suitable patients calling into question the extent to which some definitions may be overly narrow.

Negative symptoms are recognized by both the FDA (Food and Drug Administration) and EMA (European Medicines Association) as features of schizophrenia that are not adequately treated by available antipsychotic therapies and are considered a valid target for drug development (Laughren and Levin, 2006, 2011; European Medicines Agency, 2012). Given the recent increased attention to this area as an indication by itself, there is lack of clarity as how to define appropriate patients for negative symptom trials and the extent to which current medications affect negative symptoms.

There are two major ways to define negative symptom patients, based on prominent negative symptoms and the other based on predominant negative symptoms, a view adopted by EMA. The prominent view maintains that the treatment of prominent symptoms reflects the clinical reality of most patients whose illness does not have a clear prominence of either positive or negative symptoms, but may have both. The predominant view posits that only in the relative absence of one symptom group can the treatment of the other be properly measured not confounded by a possible indirect effect of improved symptoms of the other group. However, these definitions are untested in large-scale clinical trials and whether they define a meaningful subset of patients, needs to be examined.

In an attempt to examine the impact of various inclusion criteria for negative symptom trials we applied various prominent and predominant criteria to the NewMeds repository of data from second generation antipsychotics that included subjects with active positive,

* Corresponding author. Tel.: +972 54 464 3889.
E-mail address: jonathan.rabinowitz@biu.ac.il (J. Rabinowitz).

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http://dx.doi.org/10.1016/j.schres.2013.06.023

negative symptoms or both. We examined the extent to which various operational criteria for inclusion in negative symptom trials would impact patient selection and examined the effectiveness of second generation antipsychotics on patients with various definitions of negative symptoms.

1. Methods

All criteria were based on the Positive and Negative Syndrome Scale (PANSS). *Prominent* negative symptoms were operationally defined as (1) Baseline score ≥4 (moderate) on at least 3, or ≥5 (moderately severe) on at least 2 negative PANSS subscale items (Kinon et al., 2006; Stauffer et al., 2012); or (2) PANSS negative subscale: score > 3 on item 1 (blunted affect) and item 6 (lack of spontaneity and flow of conversation) and at least one third item with a score > 3 and a maximum of two items with a score > 3 from the positive subscale (Moller et al., 2004).

The following definitions of *predominant* negative symptoms were applied: (1) Baseline score ≥4 (moderate) on at least 3 or ≥5 (moderately severe) on at least 2 of the 7 negative subscale items and a PANSS positive score of <19 (Stauffer et al., 2012); (2) PANSS negative subscale score ≥ 6 points over PANSS positive subscale score (Olie et al., 2006); (3) PANSS negative subscale score of at least 21 and at least 1 point greater than the PANSS positive subscale (Riedel et al., 2005) and (4) a common sense definition, negative subscale greater than positive subscale.

EMA guidelines require predominant negative symptoms in trials to study the effect of drugs on negative symptoms. Specifically the EMA criteria regard the domain of negative symptoms as including "affective flattening, restriction in the fluency and productivity of thought and speech and in the initiation of goal directed behaviour." They specify that trials in negative symptoms must be comprised of patients with predominant and persistent negative symptoms, stable condition of illness, especially negative symptoms, presence of flat affect, poverty of speech and avolition, exclusion of major depression and to "account for effects of extra-pyramidal symptoms (EPS)" (European Medicines Agency, 2012).

Specifically, the EMA inclusion criteria are as follows: a) Predominant and persistent negative symptoms; b) Flat affect poverty of speech and avolition being present as representative of core negative symptoms; c) Stable condition of schizophrenic illness for longer than 6 months, especially of the negative symptoms. The exclusion criteria are as follows: a) Major depression; low depression scores are preferable; b) Subjects with substantially confounding extra pyramidal symptoms (EPS); c) Substantial non-compliance or substance abuse.

EMA criteria were applied in two stages. In the first stage we operationalized all criteria, other than negative symptom predominance, and in the second stage we applied three different definitions of negative symptom predominance as well as two definitions of negative symptom prominence, which were not part of the EMA definition. EMA criteria were operationalized as follows: low depression was operationalized as PANSS depression item score (G6, item 20) of moderate (4) or less; and a score higher than 1 (absent) on flat affect, poverty of speech and avolition on PANNS blunted affect (N1, item 8); Lack of spontaneity and flow of conversation (N6, item 13); and Passive/apathetic social withdrawal (N4, Item 11) (which measures "Diminished interest and initiative in social interactions due to passivity, apathy, anergy or avolition). This leads to reduced interpersonal involvements and neglect of activities of daily living." We did not use Disturbance of volition (G13, item 27), as despite its name, its content does not capture volition "Disturbance in the willful initiation, sustenance and control of one's thoughts, behaviour, movements and speech". Due to the limitations of the data in our database, we were not able to take into account "persistence of negative symptoms," "accounting for EPS" and "no exacerbation of schizophrenia in the preceding three months."

2. Data

The NewMeds repository consists of data from 29 placebo controlled RCT's of second generation antipsychotics (placebo, $n = 2200$, study drug and active control, $n = 6971$), nine studies were excluded from the present analysis as PANSS item level data was not available (placebo, $n = 1673$, drug, $n = 5721$). The repository includes anonymized patient data from AstraZeneca, Janssen Pharmaceuticals, Eli Lilly, Lundbeck, and Pfizer from placebo-controlled positive trials of SGA's approved for treating schizophrenia. All active arms of drug treatment were grouped and compared to placebo. First we analyzed the data descriptively to see how many patients met various inclusion criteria at baseline, and then after 6 weeks of treatment, and then the distribution of specific negative symptoms were examined. Then we compared the placebo vs. active treatment difference between four distinct groups of patients: those with only prominent negative, only prominent positive, prominent positive and negative and no prominent domains.

3. Results

3.1. The impact of definition on acute patients

At baseline, of the patients in these studies, 8.1% and 62.3% met criteria for either of the two definitions for prominent negative symptoms and 10.2% to 50.2% met criteria for the four definitions of predominant negative symptoms (Table 1). EMA criteria for selecting patients with predominant negative symptoms for clinical trials were met by 7.6% to 33.78% of patients. After 6 weeks of active treatment, 12.2% to 26.7% of patients met EMA criteria based on the various published definitions of predominant symptoms, and 6.7% and 25.3% met published criteria for prominent negative symptoms.

3.2. Impact of definitions in chronic and residual patients and what residual symptoms remain after current treatments of acute populations

Table 2 shows the degree of residual negative symptoms remaining after 6 weeks of active treatment. This is shown in groupings of moderate or greater, moderately severe or greater and severe or extremely severe. The results demonstrate that 30.4% were rated at least of moderate level (≥4) for Motor Retardation to 75.2% for Difficulty in abstract reasoning. The most common symptoms at week 6 are blunted affect (64.4%) and emotional withdrawal (64.6%). The incidence of the three EMA core negative symptoms among patients on active treatment, of moderate or more severity (≥4), were as follows: Blunted affect (N1) 64.4%, Lack of spontaneity (N6) 49.8%, Passive/apathetic social withdrawal (N4) 63.6%. Table 3 presents a count of residual negative symptoms of moderate or higher after 6 weeks of active treatment. Almost a third of the patients (36.2%) had no such symptoms of at least moderate severity.

3.3. Impact of treatment as a function of definition

Table 4 compares treatment response between four distinct groups of patients: those with only prominent negative, only prominent positive, both prominent positive and negative and no prominent symptoms at baseline. These groups were created based on the Kinon et al. criteria (2006). Prominent negative or positive symptoms were defined as having a score ≥4 (moderate) on at least 3, or ≥5 (moderately severe) on at least 2 items in the respective subscale. For example, if a person has a score of 4 or more on at least 3 PANSS positive items but not on negative items, they would have prominent positive symptoms. The same but in reverse (e.g. 4 or more on at least 3 PANSS negative) the person would have prominent negative symptoms. If a person had both prominent positive and negative symptoms they would be classified in the both group. If