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A novel approach to measuring response and remission in schizophrenia in clinical trials

Ahmed Aboraya [a,*], Stefan Leucht [b], Henry H. Nasrallah [c], Myrto Samara [d], Josep Maria Haro [e], Ahmed Elshazly [f], Masood Zangeneh [g]

[a] Chief of Psychiatry, William R. Sharpe, Jr. Hospital. Clinical Professor of Psychiatry, West Virginia School of Osteopathic Medicine. Adjunct faculty, School of Public Health, West Virginia University (WVU), USA
[b] Dept. of Psychiatry and Psychotherapy, Klinikum rechts der Isar, Technische Universität München, Germany Ismaningerstr. 22, 81675 München, Germany
[c] The Sydney Souers Professor and Chairman Department of Psychiatry and Behavioral Neuroscience Saint Louis University School of Medicine St. Louis MO, USA
[d] Department of Psychiatry and Psychotherapy, Technische Universität München, München, Germany
[e] Parc Sanitari Sant Joan de Déu Dr. Antoni Pujadas, 42 08830 - Sant Boi de Llobregat Barcelona, Spain
[f] Atlanticare Regional Medical Center 1925 Pacific Ave Atlantic City, NJ, USA
[g] Editor-in-Chief, International Journal of Mental Health & Addiction Consultant, Kuwait Center for Autism, Kuwait

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ABSTRACT

Background: Pharmaceutical companies conduct clinical trials to show the efficacy and safety of new medications for the treatment of schizophrenia. After the new medications are marketed, clinicians treating patients with schizophrenia discover that a considerable number of patients do not respond to these new medications. The goals of the review are to examine the methodology and design of recent antipsychotic clinical trials, identify common flaws, and propose guidelines to fix the flaws and improve the quality of future clinical trials of antipsychotic medications.
Methods: A review of recent antipsychotic clinical trials was conducted using a PubMed search. Ten recent trials published in the past four years were reviewed and their methods analyzed and critiqued.
Results: The authors identified six major methodological flaws that may explain the suboptimal response in many patients after a drug is approved. Most of the flaws are related to eligibility criteria, the misuse of the Positive and Negative Syndromes Scale (PANSS) and the lack of consensus on how to define remission, response and exacerbation in schizophrenia. Proposed guidelines for a more rigorous use of the PANSS are presented and recommendations are proposed for using uniform criteria for remission, response and exacerbation in schizophrenia.
Conclusions: The authors recommend using standardized diagnostic interviews to screen patients for eligibility criteria and using the PANSS according to the author's recommendations and the proposed guidelines. Uniform criteria to define remission, response and exacerbation are recommended for clinical trials examining the efficacy and safety of antipsychotic drugs in schizophrenia.

1. Introduction

The FDA approves new medications for the treatment of schizophrenia after pharmaceutical companies conduct clinical trials showing the efficacy and safety of the newly developed antipsychotic medications. In 2015, the FDA approved three antipsychotic medications for treatment of schizophrenia: Aristada (aripiprazole lauroxil), Rexulti (brexpiprazole) and Vraylar (cariprazine). Even though the authors of the clinical trials claimed to have demonstrated efficacy, pooled data from several clinical trials showed strikingly high rates of non-response and non-remission, contradicting the efficacy claims of the authors of individual clinical trials (Samara et al., 2016). A systematic review of current literature showed that the efficacy of second-generation antipsychotics vary from 7% to 68% in treatment-resistant schizophrenia (Molins et al., 2016). The authors, based on clinical experience of treating patients with schizophrenia, opine that a considerable number of patients do not respond to these new medications.

The current paper includes a critical review of recently published antipsychotic clinical trials with a focus on diagnoses and how psychosis, remission, response and exacerbation were measured. The goals of the review are to identify flaws in the clinical trials and to propose ways to improve future trials in schizophrenia.

2. Methods

A search for recent published clinical trials of antipsychotic medications was conducted using PubMed. The authors reviewed over 30 trials

* Corresponding author.
E-mail address: ahmed.s.aboraya@wv.gov (A. Aboraya).

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for possible inclusion. The authors selected the 10 most recently published trials as an unbiased and parsimonious representation of common flaws in the past literature, as well as current practice in research. Selecting these ten trials also avoided singling out any particular drug or research team. Clinical trials were reviewed for methodological issues, especially those involving measurement of symptoms and diagnoses.

3. Results

The following ten clinical trials were reviewed and presented: study 1 (Fleischhacker et al., 2012), study 2 (Kane et al., 2012), study 3 (Nasrallah et al., 2013), study 4 (Durgam et al., 2014), study 5 (Durgam et al., 2015), study 6 (Kane et al., 2015a), study 7 (Berwaerts et al., 2015), study 8 (Meltzer et al., 2015), study 9 (Correll et al., 2015), and study 10 (Kane et al., 2015b). The studies have been summarized in Table 1. Based upon review of the ten trials, the authors identify flaws in clinical trials and propose guidelines for a more rigorous use of the Positive and Negative Syndromes Scale (PANSS). The authors also describe and recommend the use of uniform criteria for remission, response and exacerbation in schizophrenia clinical trials.

3.1. Six flaws identified in schizophrenia clinical trials

3.1.1. Eligibility criteria (patients were recruited and diagnosed with schizophrenia without using standardized diagnostic interviews)

The poor reliability of psychiatric diagnoses has posed a serious challenge to psychiatrists, psychologists and mental health professionals for decades (Schmidt and Fonda, 1956, Kreitman et al., 1961, Beck et al., 1962, Sandifer et al., 1964, Sandifer et al., 1968, Kendell et al., 1971, Spitzer and Fleiss, 1974, Aboraya et al., 2006). To overcome this serious problem, two major and related clinical and research tracks have emerged and developed over the last six decades: diagnostic classifications and diagnostic interviews. For diagnostic classification, the World Health Organization (WHO) and American Psychiatric Association (APA) have developed and published diagnostic criteria for mental disorders; the latest editions are the International Classification of Diseases, tenth edition (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) (WHO, 1993, American Psychiatric Association, 2013). The use of diagnostic systems such as the DSM has improved the reliability of psychiatric diagnoses (Spitzer and Forman, 1979a, Spitzer et al., 1979b, Hyler et al., 1982, Spitzer and Siegel, 1990, Yutzy et al., 1995, Regier et al., 2009). In order for diagnostic systems to be used properly and reliably, standardized diagnostic interviews were developed (with questions, probes, glossaries and manuals) to guide clinicians and researchers to make diagnoses based upon the diagnostic system used (ICD or DSM) (Wing et al., 1990, Spitzer et al., 1992, Williams et al., 1992, WHO, 1994a, Sheehan et al., 1998, Aboraya et al., 2014, Aboraya, 2015, Aboraya et al., 2016). With the use of classification systems and standardized diagnostic interviews, the reliability of psychiatric diagnoses has improved (Skre et al., 1991, Basco et al., 2000, McClellan and Werry, 2000, Aboraya, 2007). Consequently, funding agents and journals consider standardized diagnostic interviews as the de facto gold standard for clinical research (Rettew et al., 2009). Among the ten trials reviewed, five studies (studies 3, 5, 8, 9 and 10) used standardized diagnostic interviews (the SCID and MINI) (Nasrallah et al., 2013, Correll et al., 2015, Durgam et al., 2015, Kane et al., 2015b, Meltzer et al., 2015). The other five studies (studies 1, 2, 4, 6 and 7) did not use standardized diagnostic interviews (Fleischhacker et al., 2012, Kane et al., 2012, Durgam et al., 2014, Berwaerts et al., 2015, Kane et al., 2015a). Without using standardized diagnostic interviews, it cannot be ascertained that patients recruited for the trial had schizophrenia and not schizoaffective, psychotic bipolar or other psychotic disorders.

3.1.2. Standardized training of investigators across sites is not stated in the articles

Kay, the author of the PANSS, recommended standardized training of the raters so that the disparity among raters does not exceed a plus or minus 1 on the seven-point items. He also stressed that training should be identical across persons and across research sites (Kay, 1991a). Muller et al. showed that at least three training sessions are recommended to achieve acceptable level of reliability (Muller and Wetzel, 1998). None of the ten trials included a statement indicating whether the investigators had standardized training on the PANSS to ensure adequate reliability, especially inter-rater reliability for individual PANSS items.

With the exception of the study by Kay (creator of the PANSS) (Kay et al., 1988), only one study has shown good inter-rater reliability for the individual PANSS items (Bell et al., 1992). Kay recommended a minimum inter-rater reliability coefficient of 0.70 for the PANSS (Kay, 1991a). Recent and well-designed studies have shown poor inter-rater reliability for many of the individual items on the PANSS (Peralta and Cuesta, 1994, Norman et al., 1996, Muller and Wetzel, 1998). In Norman et al., the raters were three psychiatrists and one clinical psychologist with almost 40 years combined experience in assessing patients with schizophrenia. Yet, three of items on the positive subscale, and all of the items on the negative subscale and general psychopathology subscales (with the exception of G9, unusual thought content), had intraclass correlations (ICC) of <0.70 (Norman et al., 1996). Consequently, Muller designed a study to demonstrate the efficacy of PANSS training and concluded that after three training sessions, 90% of the PANSS items reached an acceptable level of reliability ($K > 0.40$) and 80% of the PANSS items had values greater than $K = 0.60$ (Muller and

Table 1

	Study 1 Fleischhacker et al. (2012)	Study 2 Kane et al. (2012)	Study 3 Nasrallah et al. (2013)	Study 4 Durgam et al. (2014)	Study 5 Durgam et al. (2015)	Study 6 Kane et al. (2015a)	Study 7 Berwaerts et al. (2015)	Study 8 Meltzer et al. (2015)	Study 9 Correll et al. (2015)	Study 10 Kane et al. (2015b)
Good design parameters										
1. Used SDI	No	No	Yes	No	Yes	No	No	Yes	Yes	Yes
2. Standardized PANSS training	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
3. Used SCI-PANSS	No	No	No	No	No	No	?	?	No	No
4. Used PANSS subscales	No	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes
5. Used expert-defined criteria for remission	No	No	No	No	No	No	No	No	No	No
6. Used CGI-SCH	No	No	No	No	No	No	No	No	No	No
Poor design parameters										
1. Used PANSS total score	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Graphed PANSS total score	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Limited relapse criteria	Not used	4 criteria	5 criteria	4 criteria	4 criteria	4 criteria	4 criteria	4 criteria	4 criteria	4 criteria
4. Used CGI	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

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