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ORIGINAL PAPER

Critical trial-related criteria in acute schizophrenia studies

Michael Riedel · Stefan Leucht · Eckart Rüther · Max Schmauß · Hans-Jürgen Möller

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Abstract The Trial Criteria in Schizophrenia Working Group was convened in November 2007 to define consensus criteria for clinical trials in patients suffering from acute schizophrenia with special focus on placebo-controlled trials and withdrawal conditions. Clinical trials involving patients give rise to ethical and medico-legal dilemmas. Essential research of new drugs may potentially expose patients to ineffective treatment regimens or placebo. The complexity of the problem increases when dealing with mentally ill patients. The Working Group's criteria are thought to cover different aspects important in conducting clinical trials namely to ensure the patient's safety, to present criteria that would allow the ethics committees to agree to the proposed criteria and to enable the possibility to reasonably conduct and ensure comparable quality of clinical studies in acutely ill patients with schizophrenia. To furthermore counteract current inconsistencies, these criteria should be evaluated using standardized rating scales applying established cut-off criteria. The developed trial criteria cover inclusion and exclusion criteria as well as withdrawal criteria due to non-response or worsening of symptoms.

Keywords Schizophrenia · Clinical trial · Withdrawal criteria

M. Riedel (✉) · H.-J. Möller
Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University Munich, Nussbaumstrasse 7, 80336 Munich, München, Germany
e-mail: riedel@med.uni-muenchen.de

M. Riedel
Psychiatric Clinic, Vinzenz-von-Paul-Hospital, Rottweil, Germany

S. Leucht
Department of Psychiatry and Psychotherapy, Technical University Munich, Munich, Germany

E. Rüther
Department of Psychiatry and Psychotherapy, University of Göttingen, Göttingen, Germany

M. Schmauß
Psychiatric Clinic, District Hospital Augsburg, Augsburg, Germany

Rationale for consensus on clinical trial criteria in schizophrenia

Evidence-based medicine has become one of the most important terms in today's health system, also in psychiatry with randomized control group studies considered to be the decisive level of scientifically proven evidence as far as therapeutic aspects are concerned [1]. In such studies, the efficacy of a substance administered in patients of the experimental group is compared with the efficacy of a placebo or of a drug licensed for the same indication, or with the efficacy of both with the patients being allocated randomly either to the experimental or to the control group [2]. However, this may potentially expose patients to ineffective treatment regimens or placebo [3] bearing risks and disadvantages. Evidence-based medicine demands scientifically proven knowledge, yet this demand for research with human subjects has been often critically discussed by the public and the respective individual, a dilemma also know as "ethical paradox of therapy research" [4].

The complexity of the problem increases when dealing with mentally ill patients. As on the one hand there is no known cure for their disease and on the other hand it might

sometimes be questionable to what extent, these patients are able to provide informed consent to participate in clinical trials. Beside the Declaration of Helsinki's historical concern with especially placebo use in medical research on the moral principle that no patient should be denied the best available treatment, there are still shortcomings regarding the patient's safety due to missing study consensus criteria in cases of treatment non-response or even worsening of symptoms. On the background of the controversial discussion of the pros and cons of placebo-controlled studies, Zipursky and Darby concluded that situations may arise where the inclusion of a placebo group becomes necessary, emphasizing the need to ensure highest quality of care and to only include patients who meet the highest standards of informed consent [5].

In order to ensure highest quality of care for all patients, a standardized understanding of the patients' safety and health is needed when performing clinical trials. However, to date, a consensus on study criteria ensuring safety and efficacy is standing out. The absence of consensus criteria in schizophrenia studies also hinders cross-comparison and generalizability of study results. Even though a PANSS score of $\geq$60 points or a BPRS score of $\geq$42 points are often applied as inclusion criteria in placebo-controlled acute studies, the appropriateness of these criteria has not been examined yet and a consensus statement is still outstanding. In particular, it remains unclear across study protocols and corresponding publications at which degree of clinical status deterioration a patient should be withdrawn from the study. Withdrawal based merely on investigator's judgment is not deemed enough.

Most often, clinical trials meet the requirements of drug-licensing agencies to show that a drug works and that it is safe to use; however, such trials do not reveal much about how the new drug works in the individual or within a typical setting or other issues important to patients [6]. For long, authors have tried to emphasize the importance of ensuring the patient's safety within clinical studies given that the participant's safety is a primary concern [7]. Carpenter et al., for example, proposed different considerations for the individual protection when participating in a study [8]. The authors stated that a careful subject selection, enhanced therapeutic and clinical care monitoring, an early identification and intervention in case of symptom exacerbation, a definition of the duration of risk period and the explanation of benefits to the participant might increase the individual's safety in trial participation [8]. Others in turn have focussed on the emergence and risk of suicide in terms of drug safety concerns [9]. Therefore, there was the growing need to develop valid consensus criteria to ensure the patient's safety when participating in clinical trials, which can be applied universally when conducting research in schizophrenia patients.

As a consequence, the Trial Criteria in Schizophrenia Working Group (TCSW) was convened in November 2007 to define consensus criteria for clinical trials in patients suffering from acute schizophrenia with special focus on placebo-controlled trials and withdrawal conditions. Members of the TCSW came from academia and industry bringing together experts in clinical trial design, ethical trial issues, psychometrics, as well as research psychiatrists involved in studies of schizophrenia, and other psychiatric disorders. All academic and research psychiatrists go back to a long-time experience in planning and conducting clinical as well as placebo-controlled trials in schizophrenia patients and have worked as advisers for their local ethic committees. The process of proposing withdrawal criteria involved reviews of the literature and discussions within group sessions.

The Working Group's criteria are thought to cover different aspects important in conducting clinical trials: first of all, to ensure the patient's safety, secondly to present criteria that would allow the ethic committees to agree to the proposed criteria and thirdly to enable the possibility to reasonably conduct and ensure comparable quality of clinical studies in acutely ill patients with schizophrenia. To furthermore counteract current inconsistencies, these criteria should be evaluated using standardized rating scales applying established cut-off criteria. A standardized evaluation of psychopathological symptoms and their quantitative assessment of change over time with or without therapeutic interventions has been established in psychiatric research [10] in order to enhance comparability and generalizability of the applied treatment. The present paper is not about the discussion of the pros and cons of placebo use in acute schizophrenia studies, given its requirement by the US and EU regulatory authorities.

The Working Group decided on two established measuring instruments in schizophrenia research to evaluate the patient's safety and the need to withdraw a patient from a clinical study: The Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression Improvement Scale (CGI-I). These are two of the most widely used measures of treatment efficacy in clinical trials examining schizophrenia patients and antipsychotic medication [11]. The PANSS was developed to provide a well-defined instrument to specifically assess positive and negative symptoms of schizophrenia [12]. The PANSS is a widely used 30-item scale for the assessment of schizophrenic symptoms composed of three subscales: positive symptoms (items P1-P7), negative symptoms (items N1-N7) and general psychopathology (G1-G16). [For each item graduated on a seven-point scale [1–7], the PANSS total score ranges from 30 to 210, the positive and negative subscores from 7 to 49 and the general psychopathology subscore from 16 to 112.] The Clinical Global Impression

Improvement Scale (CGI-I) is furthermore used. The Clinical Global Impression Improvement Scale assesses how much the patient's illness improved or worsened compared with a baseline state. The CGI Improvement Scale can again be rated from 1 = very much improved up to a score of 7 = very much worse. Due to recently published linking analyses, a good framework for understanding the clinical meaning of specific PANSS scores in drug trials has been provided [13], which is a precondition of being able to define clinically relevant withdrawal study criteria.

The proposed criteria are defined for the use in studies with acutely ill patients suffering from schizophrenia with positive symptoms as primary psychopathological symptoms. Patients suffering from primary negative, depressive or catatonic symptoms show different response patterns and are specific subgroups usually not included in randomized-controlled trials.

Development of trial criteria for schizophrenia

As the inclusion and exclusion criteria of clinical trials already bear the potential of influencing the patient's safety as well as the course and outcome of the study results, consensus should start with guidance on inclusion and exclusion criteria. Generally, it is important for the patient's safety to check his capability and adequacy to provide informed consent, which has been in the focus of an important public and professional debate. Carpenter et al. stated that patients with severe schizophrenia do have decisional capacity for informed consent and those with impairments in their capability to provide informed consent were found to profit from remediation [14]. Therefore, before checking the following inclusion and exclusion criteria, the cognitive abilities of the patient should be examined and evaluated and decided on whether or not the patient is generally capable of providing informed consent.

Inclusion criteria

The diagnostic procedure should be performed by a psychiatrist or a clinician with advanced psychiatric training. Furthermore, the PANSS total score at study entry should lie between 75 and 120 points maximum. This inclusion criterion is based on the rationale that a patient should be at least moderately ill to allow the patient to respond to the treatment (quality of the study); however, the patient should not be too ill risking his/her safety. Also, it is important to include severely ill patients in clinical schizophrenia studies in order to ensure that the compound evaluated in the clinical study receives its approval without any restrictions. It is also often the most severely ill patients who respond fast to treatment. This is why the PANSS threshold should not be lower than 120 points in order to ensure that patients with severe symptoms can still be included in the clinical study. Depending on other trial characteristics (e.g., placebo-controlled versus active controlled, or comparison of two approved drugs), higher upper limits can be possible. Patients with a PANSS of 120 points or higher are still able to comply with the study procedures and are not too handicapped by psychopathological symptoms.

The PANSS total score at study entry should also incorporate two out of the four "psychotic" items (conceptual disorganization [P2], hallucinatory behavior [P3], grandiosity [P5], unusual thought content [G9]) rated with at least moderate severity (=4 points). Again, as these are core symptoms of schizophrenia, incorporating these items into the definition of inclusion criteria should ensure that the patient is acutely ill and allow the patient to respond to antipsychotic treatment. The intended patient population and the level of psychosis can be further defined via certain PANSS single items in each individual study performed. The definition of a maximum number of past illness episodes does not seem reasonable, except the study performed explicitly evaluates treatment-resistant patients. Inclusion criteria that a subject has previously responded to an adequate course of antipsychotic therapy are often applied.

Exclusion criteria

Increasing suicidality is defined as an imperative exclusion study criterion for the patient's safety cannot be guaranteed anymore. High scores on certain PANSS items (e.g., aggressiveness) are not a stand-alone exclusion criterion as long as they do not influence the patient's and/or staff's safety. Also, patients resistant to antipsychotic pretreatment (non-response to two different antipsychotic treatment regimens with adequate dosing and reasonable duration of treatment) as well as patients with clozapine treatment in their medical history (as this could also be a sign for treatment non-response) should not necessarily be excluded from study participation. A study participation of treatment-resistant and clozapine-pretreated patients should be decided on an individual basis given specific study aims and study outcome parameters.

Another important aspect for successfully conducting clinical trials is the role of the participating study centers. For well-experienced study centers with trained psychiatrists, respectively, can minimize the potential risk of clinical trials, especially when incorporating a placebo-arm. Placebo-controlled trials should therefore only be performed within an inpatient study setting, at least for the first two study weeks.

Evaluating non-response and worsening from a clinical point of view

Withdrawal criteria for clinical trials should comprise two different categories of potential risk for the participating patient. One dimension is the patient's non-response to the treatment applied and the second dimension is his/her psychopathological worsening.

Missing psychopathological improvement—non-response

Regarding non-response, the time point of evaluating this process is very important as time to response to antipsychotic treatment varies between days and weeks. According to the current hypothesis of early response, most patients respond to the antipsychotic treatment applied within 2 weeks of treatment [15, 16]. Several trials found early response after 2 weeks to be a significant predictor of subsequent treatment outcome [17, 18]. However, due to variability in approaches and measures used, whether and which degree of early non-improvement should be used for treatment decisions still need to be determined. Due to the individual time to response and the influence of the patient's personal psychiatric history, most current treatment guidelines recommend a duration of treatment of 6 weeks before changing the treatment applied [19]. The time criterion of 6 weeks of treatment for the patient to respond to antipsychotic treatment is also in accordance with recommended guidelines of the approval criteria proposed by the European Agency for the Evaluation of Medical Products [20]. However, observing the patient for 6 weeks without any treatment adaptations in non-responders might result in a generally unfavorable course of the illness. Still, given the uncertainties in terms of when and how to evaluate response to treatment and due to the fact that most controlled trials do not last for more than 6 or 8 weeks, response to treatment within this time period does not seem to be an adequate criterion to be defined as an obligatory withdrawal criterion. Instead, we rather propose to look closer at psychopathological worsening as condition for withdrawal.

Psychopathological worsening

A change in the patient's psychopathological status to the worse is defined as an obligatory withdrawal criterion. The worsening should be evaluated globally and not according to single items of a rating scale. The rating scale that most reasonably judges a potential worsening of the patient is the CGI Improvement Scale (CGI-I) as this scale is regarded as the scale most practicable and most intuitive to use for the study registrars, particularly as there is no published data, and evidence on what percentage worsening on the PANSS scale would be regarded as a valid withdrawal criterion. Since an improvement on the CGI-I scale (3 = minimally better) is considered to be clinically meaningful as it equals the mean improvement of a patient after 6 weeks of inpatient treatment, one can in turn consider a minimal worsening (score of 5) also as clinically relevant. It should be critically discussed if the patient's minimal worsening on the CGI-I scale should be considered to be a withdrawal criterion. However, a definite reason for withdrawal is given when the score on the CGI-I scale worsens not only by one point but to a score of $\geq$6 ("much worse"). If the patient's condition has worsened that much, his/her safety cannot be ensured anymore. This is especially important in placebo-controlled trials where participants on placebo should not be denied active treatment in case of such a worsening of their overall state.

However, considering current research, the CGI-I scale can be regarded as a PANSS-based scale. Psychometric procedures of equipercentile linking were used to compare the PANSS with the CGI-I scale, and the results provide a better understanding of the PANSS and can therefore help the study psychiatrist to interpret the results of the performed study ratings [13]. An increase in the CGI-I score from a 4 (no change) to a 6 (much worse) equals an increase in the PANSS by 30% or by 20 points, although this was based on relatively few data. When solely the maximum PANSS study baseline score of 120 points is exceeded, this is not regarded necessarily as a reason to withdraw the patient from his study participation. The combination of an increase in the PANSS total score and the worsening of single PANSS items was not incorporated in the definition for withdrawal criteria due to missing literature evidence and impaired practicability.

An increase in the risk of suicidality or the occurrence of suicidality for the first time during study participation is furthermore regarded as obligatory withdrawal criterion. The validity of current rating scales to judge about the risk of suicidality is thought to be critical so that the study psychiatrist's clinical judgement is given highest priority.

Ratings should be performed every week in order to allow for a close monitoring of the patient's condition. A rating of a psychopathological worsening of lower magnitude than worsening leading to immediate withdrawal criteria as stated above for two consecutive weeks should result in a withdrawal of the patient.

Conclusion

To improve the patient's safety and the study's quality, the PANSS total score at study entry should be rated between

75 (to ensure possible response to treatment) and 120 (to ensure the patient's safety) points and should at least incorporate 2 out of the 4 psychotic items of the PANSS scale. Significant suicidality at study entry is a definite exclusion criterion. The psychopathological worsening of a patient to a CGI-I score of "much worse" as well as the worsening or first time occurrence of significant suicidality are defined as imperative withdrawal criteria. Based on current treatment guidelines, non-response to the treatment within 6 weeks of treatment is not regarded as an imperative reason to withdraw the patient from a study.

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