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Quantifying Clinical Relevance in the Treatment of Schizophrenia

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Abstract

Background—To optimize the management of patients with schizophrenia, quantification of treatment effects is crucial. While in research studies, the use of quantitative assessments is ubiquitous; this is not the case in routine clinical practice, creating an important translational practice gap.

Objective—To examine the relevance, methodology, reporting and application of measurement based approaches in the management of schizophrenia.

Methods—We summarize methodological aspects in the assessment of therapeutic and adverse antipsychotic effects in schizophrenia, including definitions and methods of measurement based assessments and factors that can interfere with the valid quantification of treatment effects. Finally, we propose pragmatic and clinically meaningful ways to measure and report treatment outcomes.

Results—While rating scales are ubiquitous in schizophrenia research and provide the evidence base for treatment guidelines, time constraints, lack of familiarity with and/or training in validated assessment tools limits their routine clinical use. Simple, but valid assessment instruments need to be developed and implemented to bridge this research-practice gap. Moreover, results from

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research trials need to be communicated in clinically meaningful ways. This includes the reporting of effect sizes, numbers-needed-to-treat and -harm, confidence intervals and absolute risk differences. Some important outcomes, such as treatment response, should be reported in escalating intervals using incrementally more stringent psychopathology improvements. Nevertheless, even with quantification, it remains challenging to weigh individual efficacy and adverse effect outcomes against each other and to decide on the targeted/desired improvement or outcome, while also incorporating that in patient-centered and shared decision methods.

Conclusions—Quantification of treatment effects in schizophrenia is relevant for patient management, research, and the evaluation of health care systems. Beyond consensus about meaningful outcome definitions, reporting strategies, pragmatic tool development and implementation, the discovery of novel treatment mechanisms and related biomarkers is hoped to advance measurement based approaches in schizophrenia and thereby improve patient outcomes.

Keywords

Schizophrenia; Measurement; Quantification; Efficacy; Effectiveness; Adverse Effects; Real World

Introduction

Despite multiple advances in the management of schizophrenia, there is still an enormous need to improve our understanding and treatment of patients suffering from schizophrenia. With the development of additional pharmacologic treatment options and the availability of technological tools that are hoped to help personalize treatment[1], a careful assessment of treatment effects is needed. First and foremost, this requires the detailed clinical and research assessment of beneficial and adverse effects of the treatment options. Without quantifying these effects, clinicians are hampered when trying to decide on a given treatment strategy. While treatment guidelines are helpful[2, 3, 4, 5, 6, 7, 8] in that they synthesize research results across a number of dimensions, these guidelines can only be as accurate, detailed and generalizable as the data they are based on. Moreover, incidence rates of certain treatment effects and group means of rating scale scores can only provide a yard stick for the decision making process. Ultimately, the efficacy and tolerability of a given treatment in a given patient can only be assessed directly. However, to date, measurement based approaches are not used in the routine treatment of schizophrenia. The field needs to develop pragmatic, but meaningful tools that can be used by busy practitioners working under enormous time constraints. The era of electronic medical records makes this even more relevant, as such real world effectiveness assessments can be used in large pragmatic trials. Moreover, data base outcomes research can include more generalizable treatment groups than ordinarily involved in randomized controlled trials and also provides more detailed data than ordinary claims-based research. Nevertheless, to establish measurement based approaches in the treatment of schizophrenia, research approaches need to be adapted to real world settings, simple, but valid and clinically meaningful tools and criteria are needed, and measured outcomes need to be placed in the context of the individual patient. In addition, it is important to have the patient's perspective on what is important to him/her in weighing efficacy and tolerability as well as the relative salience of specific symptoms. Finally, the successful implementation of measurement based principles in psychiatric practice needs to find ways to overcome the not uncommon fragmentation of care of severely mentally ill patients. This includes the orchestration of psychopharmacologic, psychotherapeutic, vocational and social rehabilitative and physical medical care that usually is delivered by different people. In this case, effective communication is key, but quantified assessments can greatly help the integration of goals and identification of areas in need of further improvement and synergy.

Methods

This article summarizes methodological aspects in the assessment of beneficial and adverse effects of antipsychotics in schizophrenia. We provide information about the importance of measurement based approaches in general, and review definitions and methods of such assessments. Furthermore, we address factors that can interfere with the valid quantification of treatment effects in schizophrenia patients and how measurement based outcomes ought to be reported to be clinically meaningful. Although psychosocial interventions are of enormous importance, we focus predominantly on pharmacologic treatments since psychosocial interventions are generally given in conjunction with antipsychotics, which are the cornerstone of management to which other treatments are added.

The Importance of Measurement

Measurement is one of the most critical elements in the diagnosis and clinical management of any illness. We measure the frequency and severity of symptoms as well as their functional consequences in order to make a presumptive diagnosis. We continue to measure disease-related phenomena in the confirmation of our presumptive diagnosis and then some types of measurement become the critical element in evaluating the response to treatment and the overall course of illness. Despite the ubiquitous requirements for some degree of measurement, psychiatry as a field has been remarkable in the lack of consistent clinical training for and application of valid and reliable measurement techniques[9]. Validity refers to the ability of a diagnosis or clinical assessment to reflect the “reality” of the situation. Is the diagnosis correct according to some “gold standard” or validating criteria? Reliability refers to the characteristics of an instrument or diagnosis and those who use it to arrive at the same conclusion, score, etc. when evaluating the same patient independently. Clinicians can be “wrong” in their measurement/conclusions (poor validity), but still agree with each other (good reliability). Therefore, one has to be careful to distinguish validity and reliability from each other. They are established in very different ways. Moreover, it is also important to realize that a disorder is not defined by symptoms alone, but that either subjective distress and/or functional impairment are required.

Given the fact that there are no objective laboratory or other tests to confirm or measure psychiatric illnesses and that we depend to a large extent on patient and/or informant subjective evaluation of mental sates and behavior, the situation lends itself to considerable room for error, disagreement and lack of adequate documentation. The requirements of clinical research to ensure validity and reliability of diagnosis and clinical assessments of outcome have resulted in the development of numerous diagnostic (structured interviews) and assessment (clinician, patient and informant derived) instruments, but these are very rarely utilized in clinical practice[9]. There are a variety of obstacles (perceived and real) to implementing quantitative measure in clinical practice, but there are also important benefits to the application of such approaches (Table 1).

Every treatment decision that we make involves concepts like response, remission, relapse, etc. yet these are often used in a very inconsistent fashion without any agreement as to how they should be defined and measured. Clinicians tend to rely on global clinical judgment, which can be difficult to document or replicate. How often do we see a note in a chart which states “patient better, “or “patient has had a relapse,” without any further indication of on what these statements are based. Tremendous emphasis has been appropriately placed on the application of evidenced-based medicine throughout healthcare, but the application of evidence requires an understanding of how the evidence was gathered, how generalizable it is, and to what extent it applies to the patient before us[9]. All of these issues hinge on the

measurements and definitions involved. Below, we review some of these concepts and definitions and discuss their relevance to clinical practice.

Outcomes, Definitions and Methods

Figure 1[10] outlines common treatment goals and challenges to achieving these goals. While terms like response, resolution of symptoms, remission, recovery, relapse, treatment resistance, etc are commonly used, they are used inconsistently and definitions vary.

Treatment Response

After diagnosis and the establishment of a treatment plan, evaluating response to treatment is critical. Response can be considered to be a clinically significant improvement of the psychopathology of a patient, regardless of whether the person continues to have symptoms or not. In clinical trials, thresholds in the sense of a minimum percentage reduction from the initial score on a scale such as Brief Psychiatric Rating Scale[11] or the Positive and Negative Syndrome Scale[12] are used for this purpose. The problem is that there is no agreement as to which cut-off should be used. In the literature, at least 20%, 30%, 40%, 50% and 60% reduction from the initial score have all been applied, but the clinical meaning of the cutoffs is unclear. Several publications using data from several thousand participants who were rated simultaneously with the BPRS/PANSS and the Clinical Global Impressions Scale[13] provided some important insights to this question[14, 15, 16, 17, 18].

Equipercentile linking of percentage improvement of the BPRS/PANSS with CGI-improvement score showed that a 25% reduction of the BPRS/PANSS baseline score corresponded roughly to a minimal improvement according to the CGI, while a 50% reduction corresponded to “much improved”. As many acutely ill patients with schizophrenia often respond well to therapy, we concluded that for such patients the 50% cut-off would be a more clinically meaningful criterion than lower cut-offs. On the other hand, in very chronic or treatment resistant patients even a slight improvement might represent a clinically significant effect, justifying the use of the 25% cutoff in treatment refractory patients. Interestingly, the 20% cutoff was indeed initially used in a study of refractory patients[19], but was subsequently widely applied in studies of non-refractory subjects.

We suggested the value of displaying results on response to treatment in 25% quartiles in a table (Table 2)[17, 20, 21] Such a table covers the extreme ranges of patients whose symptoms did not change or worsened during a trial (≤0%BPRS/PANSS reduction), patients who responded at least minimally (25% BPRS/PANSS reduction), patients who were at least much improved (50% BPRS/PANSS reduction) and patients who had exceptionally good responses compared to other participants in such studies (>75% BPRS/PANSS reduction). This methodology of reporting different levels of response has already been adopted[22]. In this context, it is also reasonable to use cross-sectional “remission” criteria as a measure of response in that this would identify patients who have only mild or absent symptoms on key symptom measures[20].

Many assume that ≥75% BPRS/PANSS reduction is rare in schizophrenia. Nevertheless, in an analysis of 1870 patients in randomized amisulpride trials approximately 25% of the participants reached at least 75% BPRS reduction[21]. The advantage of such a presentation is that the reader gets an impression of the *distribution* of the response. Presenting results based on only one cutoff cannot provide such information and the choice of the cutoff remains somewhat arbitrary. It should be noted that when 1-7 scaling of the BPRS/PANSS were used the 18/30 minimum score needs to be subtracted when calculating percentage reduction from baseline[21]. For the statistical analysis of a clinical trial it is important to

choose a primary cutoff a priori to avoid problems of multiple testing. Even if only the Clinical Global Impression Scale[13] was used as a response criterion, the results could be shown in a similar fashion presenting the number of participants who were unchanged, minimally improved and much improved; or not ill, mildly ill, severely ill etc. A new version of the CGI that is specific for schizophrenia has recently been developed. The schizophrenia version uses the same items and scores, but provides clear anchors as to what "mildly ill" or "moderately ill" means. Furthermore, there are subscales for positive, negative, depressive and cognitive symptoms using the same scoring system. In contrast to the original CGI, the psychometric properties of the new version have been examined and found to be sufficient[23].

In applying the response measure in clinical practice and clinical trials, it is also important to understand the context. For example, we have recently investigated the early response paradigm, in which improvement (or rather lack of improvement) after only one or two weeks is used as a "biomarker" to predict subsequent response. In this context, the threshold that has been used for "response" is a 20% or greater improvement on the PANSS[24], but this is early response and should not be confused with ultimate response where such "minimal" improvement would be unacceptable.

Remission

Remission can be defined as a state of *absence of significant symptoms*. This is an important treatment goal. However, similarly to the different available response criteria, clinical and epidemiological studies on the frequency of remission in schizophrenia were hampered by the lack of a uniformly accepted definition. For example, a series of long-term studies suggested that many patients may be in remission or even recover in the long run [for a review, see[25], but any comparison is difficult due to the variety of definitions used. In 2005, American and European expert groups suggested a remission definition for schizophrenia[20], which has been adopted by subsequent studies[26, 27]. According to these criteria, a patient is in remission if eight items of the PANSS[12] or corresponding items on the BPRS[11] or on the Scale for the Assessment of Positive Symptoms[28] or on the Scale for the Assessment of Negative Symptoms[29] are rated as "mildly present" or better (Table 3). In addition to the severity criterion there is also a time component which requires that this low level of symptoms must persist for at least six months, although short-term trials may only apply the severity criterion on a cross-sectional basis as previously mentioned.

The rationale for the selection of the eight PANSS items was that they reflect core symptoms that are required according to DSM-IV for the diagnosis of schizophrenia. The rationale for the severity threshold "mildly present at worst" was that such mild symptoms would not interfere with a patient's psychosocial functioning. This definition is also a compromise accounting for the reality of clinical trials. Two analyses of large databases of double-blind trials showed that very few patients reach the clinical state of being fully free of symptoms[30, 31], so that a more stringent threshold ("not more than questionable symptoms" or "no symptoms at all") would not have been clinically realistic. In addition, it was also taken into consideration that there is a dimensional distribution of mild and quasi-psychotic symptoms in a subgroup of the general population, and that – for similar reasons - the remission criteria of other chronic illnesses, such as e.g. polyarthritis, also do not require the complete absence of symptoms.

Advantages and Disadvantages of Response and Remission Criteria

The difference between response and remission is that response based on a percentage BPRS or PANSS reduction from baseline does not provide information on how symptomatic the patient is at endpoint. A reduction on the PANSS from 120 to 60 points is a 50% reduction,

as is a change from 80 to 40 points. (In addition, the PANSS is an interval scale, which means that a score of 6 is not necessarily twice as severe as a score of [32].) However, the patient with a score of 60 is far more symptomatic than the patient with a score of 40, although he had an absolute change score of 60 as compared to 40 points. The remission criteria provide information as to where patients end up, i.e., are they still symptomatic? At the same time, the remission criteria do not reflect the amount of change. For example, if at baseline the participants were on the average only mildly ill, many will be in remission at the end of the trial, although there was not a major reduction in symptoms[17]. Based on the above, we suggest that the best way of reporting symptomatic outcome in schizophrenia trials is to display both measures.

Treatment Resistance

Compared to simple “non-response”, treatment resistance/refractoriness implies a more persistent lack of improvement despite adequate treatment. It is important to emphasize that adequate treatment implies adequate adherence. It is likely that many patients are inappropriately considered to be treatment resistant when they are actually non-adherent[33]. The definition is at least as complex as that of response and remission. Numerous criteria have been used (Table 4)[2, 3, 4, 5, 19, 34, 35, 36]. Most often, such criteria focus on positive symptoms, but negative symptoms, affective symptoms, disturbed behavior and cognitive dysfunction can also play a role, because are associated with psychosocial and educational/vocational dysfunction. From a conceptual point of view, such definitions can span a wide range. Such definitions are often used in research. A good example are the criteria applied in a landmark study demonstrating clozapine's superiority compared to chlorpromazine in treatment refractory patients[19]. Based on history, patients had received in the preceding five years three antipsychotics from two different classes at a dosage of at least 1000 mg/day chlorpromazine equivalents for at least 6 weeks without significant clinical improvement, and without good functioning in the last 5 years (Table 4). Cross-sectionally, the patients had a BPRS total score ≥45, were at least moderately ill according to the CGI and exhibited four at least moderately pronounced BPRS positive symptoms. Prospectively, the patients had not responded to a six-week trial with haloperidol of up to 60 mg/day (non-response was defined as < 20% BPRS reduction and BPRS total score >35 and a CGI-severity score >3). It is also important to acknowledge the attempt of an international study group which described treatment resistance by combining symptoms and social functioning on a scale from 1 (complete remission) to 7 (severe therapy resistance)[34].

However, the choice of the specific criteria will depend on the circumstances. For example, the extremely stringent criteria in the study by Kane et al[19] were necessary in the context of the reintroduction of a potentially life-threatening antipsychotic drug (i.e., clozapine and its risk for agranulocytosis). Nevertheless, at least in schizophrenia practice guidelines, a certain consensus regarding criteria for treatment resistance seems to emerge (Table 4)[2, 3, 4, 5, 19, 34, 35, 36]. The American Psychiatric Association guideline[2] defines treatment resistance as “little or no symptomatic response to multiple (at least two) antipsychotic trials of an adequate duration (at least 6 weeks) and dose (therapeutic range)”. Other important guidelines such as that by the National Institute for Clinical Excellence (NICE)[3], the World Association of Societies of Biological Psychiatry[4], or those of other national psychiatric associations present similar definitions (Table 4).

Relapse

Relapse is another important outcome measure, as it often triggers a change in treatment or locus of care. Relapse can be caused by many different factors ranging from comorbid substance abuse to non-adherence, but might also mean that a patient has “broken through”

medication. (On some level, a patient who relapses despite taking an adequate dose of antipsychotic medication could be considered to be treatment resistant, but, that is not how the latter term is usually employed.) Since relapse implies an exacerbation or recurrence of symptoms, the critical question is what degree of worsening or what threshold of signs and symptoms is necessary before triggering such a classification? Should the degree of worsening imply a change in functional status or is a purely symptomatic definition sufficient? Relapse is a commonly used outcome measure in clinical trials intended to investigate the efficacy and effectiveness of treatments in the intermediate and long-term management of schizophrenia. Again, the context of use of the term relapse is important, as a trial which includes a placebo arm might have different relapse criteria than an active-active comparator trial in that, from an ethical standpoint, one would want to minimize the risks associated with placebo, while still maintaining the overall goals of the trial. In addition, it is clear that symptoms can wax and wane in schizophrenia without being sufficiently impactful to consider that a relapse has taken place.

The degree of variability in relapse rates seen across studies with similar entry criteria (Table 5) also suggests that patient populations as well as clinician/rater behavior can be different even within the same general protocol design. Although relapse does not necessarily require a change in functional status, many criteria include a change in treatment requirements, intensity of services or locus of care. These in turn are influenced by functional considerations, as are to some extent the severity ratings of specific domains of psychopathology (i.e., a symptom which influences behavior/functioning is a more severe symptom than one which does not). Table 5[37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53] provides examples of relapse criteria that have been used in recent studies.

It is also important to note that in some studies hospitalization is used as a proxy for relapse. Since hospitalization can be influenced by many environmental and health economic factors, those influences must be kept in mind as well when hospitalization is equated with relapse. In addition, not all patients who worsen and get close to a relapse need to be hospitalized, as appropriate treatment changes can be made to avoid this. For example, in a study of patients with recent-onset schizophrenia, which examined the clinical course following antipsychotic discontinuation, 96% of the patients experienced an exacerbation or relapse within 2 years, whereas only 13% were hospitalized[54].

Recovery

Recovery is an outcome domain, which much more clearly requires functional measures. This is a term that has taken on particular salience with patients and families - as well it should. Health care providers are at times focused on symptoms and signs to the exclusion of functioning and quality of life. The recovery criteria in schizophrenia are to some extent the most meaningful possible outcome measure. At the same time, however, criteria for recovery are not only influenced by the availability of psychosocial treatments, family and community supports, but also by supportive employment and supportive education as well as available jobs, etc.

Liberman and Kopelewicz[55] reviewed different criteria for recovery[56, 57, 58, 59] (Table 6). The recovery criteria proposed by Liberman and colleagues[57] have been referred to as the UCLA criteria that subsequently have been applied in outcome studies[27, 60].

Patient Reported Outcomes

Increasing attention has been focused in recent years on the importance of patient reported outcomes in informing research results and clinical practice[61]. The U.S. Food and Drug

Administration[62] defines these measures as “any report coming directly from patients about a health condition and its treatment”. Given the subjective nature of many aspects of psychopathology, it is particularly important in psychiatry to have this perspective. Yet at the same time, in schizophrenia there are concerns about insight, cognitive dysfunction, reality testing and communicative ability, which must be recognized in the acquisition and interpretation of such data. It is also important to recognize the role that such data play in the process of shared decision-making.

Traditionally, clinicians have been more focused on the alleviation and control of illness symptoms and disease treatment, rather than on adverse effects, subjective well-being and quality of life[63]. An emphasis on self report also contributes to enhanced patient self-esteem and a sense of empowerment. In addition to symptoms, adverse effects and quality of life self-report measures can also provide insight into the patient's knowledge of his/her illness and the treatments being prescribed and into other areas, such as access, quality of care, health system issues, etc.

It is beyond the scope of this paper to review the various constructs involved in the generation of these instruments or the various characteristics of specific instruments. In addition, further work needs to be done to better understand the relationship between clinician-rated and patient- rated outcomes in order to inform their most appropriate utilization and interpretation. It would also be important to determine the value of these measures as predictors of various aspects of outcome including treatment acceptance and adherence as well as overall response, relapse, long-term outcomes, tolerability of adverse effects, etc.

Table 7 provides a selected overview of relevant self report instruments that have been used in studies of patients with schizophrenia[64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89]. Some scales take relatively little time to complete, making them amenable to being used in the waiting room of mental health clinics and doctor's offices. As always, the choice and interpretation of specific measures will be influenced by the goals of the study or data collection, the characteristics of the patient population, phase and severity of illness, etc.

Clinical Relevance of Outcomes in Schizophrenia

In order to establish the clinical relevance of treatment effects, clinicians should carefully assess and quantify efficacy and adverse effects using direct questioning of patients (see below) and, as much as is practical, also using rating scales. In research studies, validated scales should always be employed, both for therapeutic as well as for adverse effect outcomes. Moreover, adherence and attitudes toward medications that can be used to identify patients at high risk for non-adherence, such as the Drug Attitude Inventory[69] should be considered, as non-adherence affects both efficacy and tolerability outcomes.

In addition to selecting the most appropriate assessment tools for the patient's condition and setting, a clinically meaningful display of the data beyond statistical significance should be mandatory in research reports. This includes the reporting of 95% confidence intervals or interquartile ranges around point estimates, as well as the calculation of effect sizes and numbers-needed-to-treat/harm (NNT/NNH). In general, effect sizes of 0.2 or less are considered not clinically relevant, 0.5 is a medium effect size and effect sizes of 0.8 and above are considered large[90]. Point estimates with non-overlapping 95% confidence intervals are considered significantly different. Moreover, to establish clinically meaningful effect sizes for categorical outcomes of benefit or harm, NNTs/NNHs should be calculated as the inverse of the absolute risk difference (i.e., 1 divided by the delta between the proportion of patients having a certain outcome in one group compared to the other group).

NNTs/NNHs of 1-3 represent a large effect size, 4-6 are medium and 7-10 are small[91]. Furthermore, Likert-type scales that provide ordinal, rather than nominal, data are frequently used in psychiatry. Although each ordinal data point can be converted into a numeric value for ease of data entry (e.g., the CGI scale goes from 1-7), it is important to note that these are not continuous data and that nonparametric, not parametric, statistical tests should be employed in the analysis of such results.

Notwithstanding these general principles, the translation of such mathematical quantification into clinical relevance is not straightforward. This complication is due to the fact that effect sizes for certain efficacy or adverse effect outcomes might be weighted rather differently based on how critical the improvement or intolerability for a given individual is, i.e., how much it affects subjective well-being, quality of life, functioning, health and longevity. Such risk-benefit evaluation must be made on a case-by-case basis and evaluations might change over time, even for the same physician or patient and his/her family[92].

Clinical Measurement of Efficacy in Schizophrenia

A number of rating scales and assessment batteries have been validated that are used frequently in clinical pharmacology trials in schizophrenia. While the use of efficacy rating scales is commonplace in research settings, there exists a big research-practice gap regarding the routine implementation of measurement based principles in clinical care. As mentioned above, this is due to a variety of factors, with time constraints and lack of familiarity and training being among the most important ones. Thus, the field, administrators and regulators need to decide which outcome measures are most appropriate that can be realistically implemented in routine clinical practice. Ideally, abbreviated, pragmatic but meaningful scales should be developed and field tested to identify those that could become standard of care.

We propose that, at a minimum, the Clinical Global Impressions (CGI) severity and improvement scale [13] and the Global Assessment of Functioning (GAF) scale[93] should be used and documented at each clinical visit (Table 8). While the administration of the entire BPRS[11] or PANSS[12] is likely not practical in most busy clinical settings, the assessment and documentation of the eight items from the PANSS (or the equivalent items from the BPRS) that are used to define remission in patients with psychosis[20] is a reasonable expectation, as a clinical interview should focus on each of these items anyway (i.e., delusions, hallucinations, social withdrawal/anhedonia), with four if these being merely observational (formal thought disorder, bizarre behavior, alogia and blunted affect) (Table 3). Nevertheless, training on the anchored assessment needs to be provided.

In addition, the clinical assessment should also include the specific PANSS (or BPRS) item “hostility”, as this item has been shown to be predictive of overt physical aggression (or violence) against other persons. For example, in schizophrenia patients in the CATIE trial, for each unit increase on the 7-point rating of hostility, the odds of serious violence increased significantly by a factor of 1.6[94]. Hostility and related violent behaviors are clinically relevant since they constitute a frequent reason for hospital admission (being reflected in some criteria for relapse), delay discharge, and increase the burden of illness for families and caregivers. Finally, assessing hostility and violence in schizophrenia has important treatment implications[95, 96, 97, 98].

Cognitive deficits are a core feature of schizophrenia and appear to be particularly related to poor functional outcomes[99, 100, 101, 102]. Although the development of interventions to improve the cognitive deficits in schizophrenia has become a major target, antipsychotics have minimal effects and, to date, no selective treatment has been identified. Key areas of the cognitive deficits in schizophrenia include: attention/vigilance, processing speed

working memory, verbal memory, visual memory, reasoning and problem solving, executive functioning and social cognition[99]. A number of neurocognitive test batteries exist (Table 9) [99, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115]. However, these formal tests are usually labor and time intensive and require special training for the administration and scoring. While the mini mental status examination can be used to assess gross cognitive abnormalities, it is too crude to be useful for the assessment of deficits that are below the level of those observed in delirium or dementia. As part of the general mental status examination, a number of attention, memory and reasoning capabilities are crudely assessed by use of the serial 7 (or 3) subtraction, 5 minute 3-word recall, the request to link words through overarching categorical similarities and explain proverbs. Beyond this, few parent, teacher and/or clinician reports/questionnaires are available [114] or under development [115] that could prove to be helpful to provide an office based opportunity to assess cognitive deficits cross-sectionally and over time, which could include beneficial or adverse medication effects on clinically relevant, real world cognitive functioning.

Regarding related psychopathology, such as depression and anxiety, at a minimum, a global, two-item assessment of “observed” and “reported” severity of these domains should be ascertained and reported using a 10-point visual analogue scale or a Likert-like scale (none, mild, moderate severe, extreme). Neuro-vegetative signs (appetite, sleep, activity level) should also be part of a regular clinical interview and should be quantified in the same way. Areas of high clinical importance for the safety of the patients and of others, i.e., suicidality and homicidality should also always be inquired about. It is recommended that medical records be equipped with such simple rating tools and that clinicians have to fill out these scales before being able to move on to another page when using electronic medical records. Obviously, in settings with more time and depending on the aim, formal rating scales can also be employed for depression[116, 117, 118] and anxiety[119].

While quality of life and functional outcomes are increasingly relevant as treatment aims, there are currently no simple tools to measure these outcomes, as available interview-based scales are lengthy [e.g., [120]] and simpler self reports [e.g., [84]] may lack detail and be too insensitive. Thus, qualitative statements about who the patient lives and interacts with, how many times per week social contacts take place outside of the immediate family, whether the patient can provide self care and what the voluntary or paid employment status is should be inquired about and recorded at regular time intervals. These areas are useful to assess, as they overlap with proposed psychosocial recovery criteria reviewed above[57]. Furthermore, to document treatment decisions, inefficacy in specific domains should be recorded as a justification to switch or augment any given treatment. Finally, adherence also needs to be inquired about and quantified, so that efficacy patterns can be evaluated more objectively.

Clinical Measurement of Adverse Effects in Schizophrenia

Antipsychotic treatment is associated with a wide range of acute and long-term side-effects that can impact on psychiatric and physical health, adherence, subjective well-being and quality of life[121]. However, identifying side-effects and attributing them to a particular drug can be difficult because patients are frequently on more than one medication and cannot always describe the onset and circumstances of their experiences in detail. Some patients with schizophrenia are not even aware that certain experiences can be a drug effect, requiring counseling when initiating treatment. Some domains, such as sexual side-effects and constipation, are less readily volunteered and patients may only report these side effects when directly questioned about them[122].

Moreover, it can be difficult to distinguish some adverse effects from illness symptoms, e.g. Parkinsonism from negative symptoms or depression, and akathisia from agitation[123]. Side-

effects are best assessed by using a standardized rating scale and a number of global and specific rating scales are available (Table 8). Some measure specific side-effects, such as the Barnes Aktathisia Ratings scale for assessing akathisia[124], the Simpson Angus Scale[125], Extrapyramidal Symptom Rating Scale [126] or the Abnormal Involuntary Movement scale[127], whereas others, such as the Udvalg for Kliniske Undersøgelser (UKU) scale or the Treatment Emergent Side Effect Scale (TESS)[13], provide an overview of side-effects[128]. Side-effects are not simple dichotomous variables and their presence differs among subjects. Therefore, rating scales should include thorough anchors for the score of each item. Moreover, the severity, attribution to a given medication and onset and offset need to be captured. Furthermore, rating scales generally only assess the presence and severity of a side-effect, but not whether the side-effect is subjectively bothersome or associated with functional impairment, although quality of life is more affected by the subjective feeling of a side-effect than the number of side-effects[129]. Some patients feel sedation as a bothersome side-effect whereas others are not particularly bothered by it and may even see this as a desired effect. Both past and present side-effects have a negative impact on compliance which should encourage psychiatrists' to do their best to avoid, monitor and manage adverse effects in order to optimize treatment outcomes[130].

In clinical trials, most frequently adverse effect are assessed by means of general, open ended and unstructured questioning, rather than by rating scales. This is supposedly done to reduce the background noise of symptoms not associated with a given treatment or not reaching the level of subjective relevance. However, some symptoms might have been relevant and are not reported due to cognitive difficulties or feelings of shame, or lack of knowledge that a symptom could be related to a medication. Moreover, in many trials, the absence of rating scale assessed side effects is used as a justification to solely report frequencies, but not statistically analyze and compare them against control conditions. This has remained the case in regulatory trials performed to gain approval or indications. This is an obvious bias against a state-of-the art assessment of adverse effects that are not treated the same way as efficacy outcomes. In fact, a recent systematic review of adverse effect reporting in 167 antipsychotic clinical trials in schizophrenia-spectrum disorder patients published in English between January 2002 and July 2007 with available efficacy and/or adverse effect reporting found that safety and tolerability data were collected and reported in mostly non-standardized ways, which does not allow a fair and meaningful comparison of the relative risk profiles of individual antipsychotics[131]. Across these studies, EPS and weight gain were most frequently assessed, but a minority of studies included reporting of metabolic abnormalities, negative subjective experiences and sexual dysfunction. Published rating scales were frequently used to evaluate EPS, but systematic methods were rarely applied to any other treatment-emergent problems. Moreover, the definition of individual adverse effects and the method of reporting were inconsistent[131].

We propose that, at a minimum, key adverse areas that should be inquired about in patients treated with antipsychotics (sedation, EPS, dyskinesia, sexual functioning) should be quantified either along a 10-point visual analogue scale or using a Likert-like scale (none, mild, moderate severe, extreme). Furthermore, Parkinsonian side effects and abnormal involuntary movements should be measured directly at least twice per year, using the Simpson Angus Scale[125] or the ESRS[126], the Barnes Akathisia Scale[124] and the AIMS[127] (Table 8). This takes less than 5 minutes when both the clinician and patient are familiar with this assessment. In addition, cardiometabolic indices, such as body weight, body mass index, waist circumference and fasting glucose and lipids, should be measured and documented at currently recommended time intervals[132]. Implementation of monitoring guidelines can be difficult[133], but low-cost, strategic and administrative interventions can help increase guideline compliance. Finally, as for efficacy, to document treatment

decisions, intolerability in specific areas should be recorded as a justification to switch or augment any given treatment.

Summary and Conclusions

Quantification of treatment effects has relevance for patient management, research, and overall health care. Optimized treatment of schizophrenia aims for improvements in symptoms, subjective well being and functioning, while minimizing adverse effects that interfere with treatment success. Clinical decision making requires the standardized definition of treatment goals and outcomes, and the quantification of efficacy, adverse effects and overall effectiveness to inform what degree of improvement in target domains is sufficient, what type and severity of adverse effects are still acceptable and what functional outcomes are sought. Rational decisions about dose adjustments, when to stop a medication, when to switch or augment treatments, etc require measurement based approaches. While rating scales are ubiquitous in schizophrenia research, time constraints, lack of familiarity with and training in validated assessment tools has limited their routine use in clinical practice. Easy to use but meaningful rating scales need to be developed and implemented to bridge the gap between lengthy rating scales used in research trials and mostly unstructured, qualitative assessments employed in clinical practice. Moreover, results from research trials providing the evidence base that guide practice need to be communicated in clinically meaningful ways. This includes going beyond the mere reliance on statistical significance. Pragmatic quantification should always include the reporting of effect sizes, numbers-needed-to-treat and -harm for meaningful categorical outcomes, confidence intervals, and absolute risk differences. Some important outcomes, such as treatment response, should be reported in escalating intervals using incrementally stringent psychopathology improvements.

Nevertheless, even despite quantification, it remains a challenge to weigh individual efficacy and adverse effect outcomes against each other and to decide on the targeted maximum improvement or outcome. Subjective, patient-based ratings and shared decision making need to be integrated with measurement based approaches. Finally, beyond consensus about meaningful outcome definitions, reporting strategies and pragmatic tool development and implementation, the discovery of novel treatment mechanisms and biomarkers is hoped to further advance measurement based approaches in schizophrenia and improve patient outcomes in the near future.

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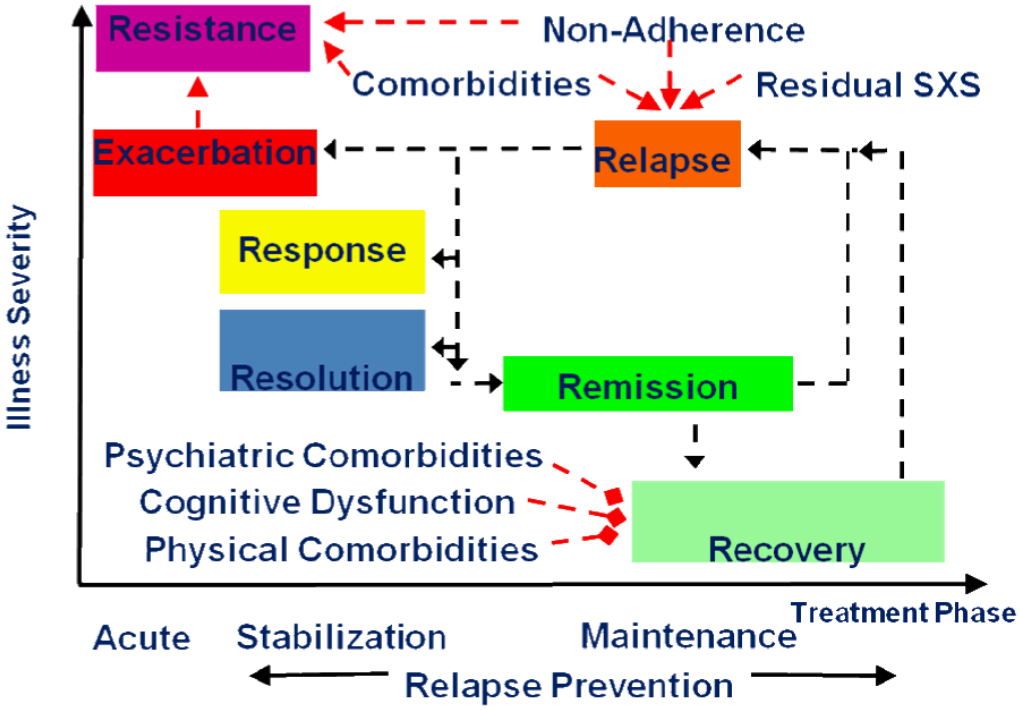

Figure 1.
Treatment Goals and Challenges [10]
Adapted from: Kane JM and Correll CU. Dialogues Clin Neurosci. 2010;12(3):345-57 [10]

Table 1

The Value of and Barriers to Implementing Measurement Based Approaches in Psychiatry

Value of Measurement Based Approaches	Barriers to Measurement Based Approaches
Contribution to diagnostic process	Inadequate appreciation of benefit
Establishing baseline severity	Perceived value of global judgment
Providing targets and treatment goals	Time constraints
Evaluating the efficacy of treatment	Lack of appropriate instruments
Evaluating tolerability and adverse effects	Inadequate training
Influencing level of care	Reimbursement concerns
Medical record documentation	

Table 2

Suggested Presentation of Range of Response and of Remission Rates in Clinical Trials [17, 20, 21]

Presentation of Responder and Remission Rates based on Percentage Change on the Positive and Negative Syndrome Scale (PANSS)[12] or the Brief Psychiatric Rating Scale (BPRS)[11]								
Criteria	**Total n**	**≤0% PANSS/BPRS reduction**	**>0% - 24% PANSS/ BPRS reduction**	**25% - 49% PANSS/BPRS reduction**	**50% - 74% PANSS/BPRS reduction**	**75% - 100% PANSS/BPRS reduction**	**Remission***	
Intervention Group	N	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Control Group	N	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Presentation of Responder and Remission Rates based on Clinical Global Impressions (CGI) Improvement and Severity Scores[13]								
CGI-improvement score	**Total n**	**Very much worse**	**Much worse**	**Minimally worse**	**unchanged**	**Minimally improved**	**Much improved**	**Very much improved**
Score		7	6	5	4	3	2	1
Intervention Group	N	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Control Group	N	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
CGI-severity score	**Total n**	**Extremely ill**	**Severely ill**	**Markedly ill**	**Moderately ill**	**Mildly ill**	**Borderline mentally ill**	**Normal, not at all ill**
Score		7	6	5	4	3	2	1
Intervention Group	N	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Control Group	N	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

Modified from: Leucht et al. 2007 [21]; Leucht & Kane 2006 [17];

*based on Andreasen et al 2005 [20]

Table 3

Proposed items for remission criteria as defined by the Remission in Schizophrenia Working Group (Andreasen et al 2005 [20])

		Scale for Assessment of Positive Symptoms (SAPS)[28] and Scale for Assessment of Negative Symptoms (SANS)[29] Items		Positive and Negative Syndrome Scale (PANSS)[12] Items		Brief Psychiatric Rating Scale (BPRS)[11] Items	
Dimension of Psychopathology	**DSM-IV Criterion**	**Criterion**	**Global Rating Item Number**	**Criterion**	**Item number**	**Criterion[b]**	**Item number**
Psychoticism (reality, distortion)	Delusions	Delusions (SAPS)	20	Delusions	P1	Grandiosity	8
	Hallucinations	Hallucinations (SAPS)	7	Unusual thought content	G9	suspiciousness	11
				Hallucinatory behaviour	P3	Unusual thought content	15
						Hallucinatory behaviour	12
Disorganization	Disorganised speech	Positive formal thought disorder (SAPS)	34	Conceptual disorganization	P2	Conceptual disorganization	4
	Grossly disorganised or catatonic behaviour	Bizarre behaviour (SAPS)	25	Mannerisms/posturing	G5	Mannerisms/posturing	7
Negative symptoms (psychomotor poverty)	Negative symptoms	Affective flattening (SANS)	7	Blunted effect	N1	Blunted affect	16
		Avolition-apathy (SANS)	17	Social withdrawal	N4	No clearly related symptom	
		Anhedonia-asociality (SANS)	22	Lack of spontaneity	N6	No clearly related symptom	
		Alogia (SANS)	13				

[a] For symptomatic remission, maintenance over a 6-month period of simultaneous ratings of mild or less on all items is required. Rating scale items are listed by item number

[b] Use of BPRS criteria may be complemented by use of the SANS criteria for evaluating overall remission

The PANSS scale is the simplest instrument on which a definition of symptom remission can be practically based.

DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, fourth edition

Table 4
Criteria for treatment resistance according to a selection of authors and guidelines

Reference	Definition
Kane et al 1988 [19]	Historical: no period of good functioning or significant symptomatic relief within preceding 5 years despite at least two courses of antipsychotics (doses:≥ 1000 mg/day chlorpromazine) for 6 weeksCross-sectional: BPRS score ≥ 45, score of ≥ 4 on at least two of the following factors: conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought contents, CGI score of ≥-4Prospective: 6-week trial of haloperidol-(60mg/day) fails to reduce BPRS by 20% or to below 35, or fails to reduce CGI to below 3
Brenner et al 1990 [34]	Seven levels of treatment response incorporating evaluation of symptomatology, personal and social adjustment: level 1, clinical remission; level 2, partial remission; level 3; slight resistance; level 4, moderate resistance; level 5, severe resistance; level 6, refractory; level 7, severely refractory
Meltzer 1990 [35]	At least in theory every patient who has not fully recovered to his premorbid level of functioning should be regarded as treatment refractory
National Institute for Clinical Excellence 2003 [3]	Treatment resistance is suggested by a lack of satisfactory clinical improvement despite the sequential use of the recommended doses for 6–8 weeks of at least two antipsychotic drugs, at least one of which should be an atypical.
American Psychiatric Association, Lehman et al 2004 [2]	Treatment resistance is defined as little or no symptomatic response to multiple (at least two) antipsychotic trials of an adequate duration (at least 6 weeks) and dose (therapeutic range).
World Federation of Societies of Biological Psychiatry, Falkai et al 2005 [4]	Treatment resistance is assumed if there is either no improvement at all or only insufficient improvement in the target symptoms, despite treatment at the recommended dosage for a duration of at least 6/8 weeks with at least two antipsychotics, one of which should be an atypical antipsychotic.
Australian National schizophrenia guideline, McGorry 2005 [5]	Two adequate trials (at least 6 weeks of 300–1000 mg in CPZ equivalents) of antipsychotic medication, of which at least one agent should be atypical, should have been conducted.
International Pharmacological Algorithm Project 2006 [36]	1) No period of good functioning in previous 5 years; 2) prior non-response to at least 2 antipsychotic drugs of two different chemical classes for at least 4-6 weeks each at doses ≥ 400 mg equivalents of chlorpromazine or 5 mg/day risperidone; 3) moderate to severe psychopathology, especially positive symptoms: conceptual disorganization, suspiciousness, delusions or hallucinatory behavior. IPAP also recommend considering patients as treatment resistant if they exhibit persistent psychotic symptoms, recurrent mood symptoms, repeated suicide attempts or suicidal ideation, uncontrolled aggressive behavior, moderate- severe negative symptoms or moderate-severe cognitive impairment after the adequate treatment mentioned above.

Table 5

Relapse Definition in Trials Comparing Oral Second-Generation Antipsychotics to Placebo or to First-Generation Antipsychotics

Study	Domains of Relapse Definition			
	Hospitalization	**CGI [13]**	**PANSS [12] or BPRS [29]**	**Clinical Symptoms and Others**
Dellva 1997 [37]; Tran 1998 [38]; De Sena 2003 [39]	hospitalization	-	-	-
Cooper 2000 [40] *a,b,c*	hospitalization	CGI-S ↑ ≥2	2 of BPRS-P subscale ↑≥2	-
		CGI-S ↑ ≥2	2 of BPRS-P subscale ↑≥2	-
		CGI-S ≥6	-	Need observation if patient is inpatient
Csernansky 2002 [41]; Schooler 2005 [42]	hospitalization	CGI-C ≥6	PANSS-T ↑≥25%, or +10	Self-injury, suicidal/homicidal ideation, violence
Arato 2002 [43]	-	CGI-C ≥6	PANSS P7+/-G8 ≥6 in 2 successive days	-
Beasley 2003 [44]	hospitalization	-	any BPRS-P subscale ≥4 and BPRS specific subscale ↑≥2, or positive subscale↑≥4	Completed suicide or a serious suicide attempt
Piggot 2003 [45]	-	CGI-C ≥5	PANSS P7/G8 ≥5 on 2 successive days or PANSS-T ↑ ≥20%	-
Lieberman 2003 [46]; Green 2006 [47]	-	CGI-S ≥4	Any of PANSS P1, 2, 3, 5, 6 ≥4	-
Lecrubier 2006 [48]	hospitalization	-	PANSS-T ↑≥30%	-
Peuskins 2007 [49]	hospitalization	CGI-C ≥6	PANSS-T ↑≥30%	Need for additional AP
Kramer 2007 [50]	hospitalization	CGI-S ≥4 or 3→5	PANSS-T ↑≥25% or 10 points, or specific PANSS item 3→5 or 4→6	Self-injury, suicidal/homicidal ideation, violence
Gaebel 2007 [51] *a*	-	CGI-C ≥6	PANSS-P ↑>10	GAF ↓>20
Kane 2008 [52]	hospitalization	CGI-S↑ ≥2	-	Discontinuation due to lack of efficacy
Crespo-Facorro 2010 [53]	hospitalization	CGI-S ≥6 and CGI-C ≥6	Any key BPRS subscale ≥5	Completed suicide attempt

BPRS-P=brief psychotic rating scale positive symptoms score; CGI-C/S=clinical global impression change/severity score; GAF=global assessment of functioning; PANSS-P/T=positive and negative symptom scale positive/total score; ↑=increase; ↓=decrease;

a patients required to meet all criteria concurrently;

b CGI and BPRS criteria both required to be present at 2 consecutive assessments over 3 days;

c hospitalization, CGI and BPRS criteria required to be present at the same assessment time point;

d all criteria required to be present at two consecutive visits

Table 6
Selection of Recovery Criteria in Patients with Schizophrenia

	Study And Proposed Remission Criteria for Schizophrenia			
Variable	Harding et al. 1987 [56]	Liberman et al. 2002 [57]	Torgalsboen et al. 2002 [58]	Whitehorn et al. 2002 [59]
Psychopathology	Symptom free and not taking psychotropic medications	BPRS score of </=4 on all positive and negative psychosis items	No psychiatric hospitalizations for 5 years	PANSS score of </=4 on all scales
Psychosocial Functioning	Social life indistinguishable from that of neighbors; holding a job for pay or volunteer	At least-half time work or school; independent management of funds and medications; once weekly socializing with peers	Global Assessment of Functioning (GAF) Score >/=65	Global Assessment of Functioning (GAF) Score >/=50
Required Duration	Not Listed	2 Years	5 Years	2 Years

Table 7
Selected Self Report Measures Scales for Patients with Schizophrenia

Domains	Name	Reference	# of items	Administration Time
Symptom	Brief Symptom Inventory (BSI)	Derogatis 1992 [64]	53	10
	Symptom Checklist-90-R (SCL-90-R)	Derogatis 1983 [65]	90	15
	Hamilton Program for Schizophrenia Voices Questionnaire (HPSVQ)	Van Lieshout and Goldberg. 2007 [66]	9	10
	Insight Scale	Birchwood et al.1994 [67]	32	10
Attitude towards treatment/Care	Drug Attitudes Inventory (DAI-30/10)	Awad 1993 [68]; Hogan 1983 [69]	30/10	15/5
	Camberwell Asssessment of Need (CAN)	Phelan et al. 1995 [70]	22	15
	Camberwell Asssessment of Need Short Appraisal Schedule (CANSAS)	Slade et al. 1999 [71]	22	5
	Verona Service Satisfactioni Scale (VSSS)	Ruggeri and Dall'Agnola. 1993 [72]	82	30
	Scale To Assess the Therapeutic Relationship (STAR)	McGuire-Snieckus et al. 2007 [73]	12	10
Recovery	Mental Health Recovery Measure (MHRM)	Yound and Bullock 2003 [74]	30	15
	Recovery Assessment Scale (RAS)	Giffort et al.1995 [75]	41	30
QOL/subjective well-being (for psychiatric disease)	Lancashire Quality of Life Profile (LQOLP)	Oliver et al. 1997 [76]	105	45
	Personal Evaluation of Transitions in Treatment (PETIT)	Voruganti and Awad. 2002 [77]	30	5
	Quality of Life Questionnaire in Schizophrenia (S-QoL)	Auquier et al. 2003 [78]	41	15
	Subjective Wellbeing under Neuroleptic Treatment Scale (SWN original/short form)	Naber 1995 [79]; Naber et al. 2001 [80]	38/20	20/10
QOL (generic)	World Health Organization Quality of Life Assessments (WHOQOL-100/ BRIEF)	WHOQOL group 1998 [81]	100/26	45/10
	36-Item Short Form Health Survey (SF-36)	Ware and Sherbourne 1992 [82]	36	15
	EQ-5D	EuroQOL group 190 [83]	5 items + 1 visual analogue scale	5
	Sheehan Disability Scale (SDS)	Sheehan et al. 1983 [84]	3 visual analogue scales + 2 items	3
Others	Psychological Stress Index (PSI)	Tso et al. 2011 [85]	18/9	10/5
	Self Esteem Scale	Rosenberg 1965 [86]	10	10
	Sense of Coherence Scale (SOC)	Antonovsky 1987 [87]	29	20
	Knowledge About Schizophrenia Questionnaire (KASQ)	Ascher-Svanum 1999 [88]	25	20

Domains	Name	Reference	# of items	Administration Time
	Approaches to Schizophrenia Communication Self-Report (ASC-SR)	Approaches to Schizophrenia Communication (ASC) Steering Group 2001 [89]	18	10

Table 8

Commonly Used Rating Scales To Assess Key Efficacy and Adverse Effect Outcomes in Patients with Schizophrenia

Efficacy		Adverse Effects	
Domain	**Commonly Used Rating Scale**	**Domain**	**Commonly Used Rating Scale**
Global Outcome	Clinical Global Impressions (CGI) Severity and Improvement Scale [13] Global Assessment of Functioning (GAF) Scale [93]	General	Udvalg for Kliniske Undersøgelser (UKU) [128] Treatment Emergent Side Effect Scale (TESS) [13]
General Psychopathology (including Positive and Negative Symptoms)	Brief Psychiatric Rating Scale (BPRS) [11] Positive and Negative Syndrome Scale (PANSS) [12]	Sedation	Agitation-Calmness Evaluation Scale (ACES) [134]
Positive Symptoms	Scale for the Assessment of Positive Symptoms (SAPS) [28]	Sexual	Arizona Sexual Experience Scale (ASEX) [135]
Negative Symptoms	Scale for the Assessment of Negative Symptoms (SANS) [29]	EPS overall	Simpson-Angus Rating Scale for Extrapyramidal side-effects [125]Extrapyramidal Symptom Ratings Scale (ESRS)[126]
Aggression/Agitation	PANSS Excited Component subscale or PANSS/ BPRS “hostility” item[11, 12]	Akathisia	Barnes Akathisia Rating Scale (BARS) [124]
Depression	Calgary Depression Rating Scale [116] Hamilton Depression Rating Scale (HAM-D) [117] Montgomery-Asberg Depression rating Scale (MADRS) [118]	Dyskinesia	Abnormal Involuntary Movement Scale (AIMS) [127]
Anxiety	Hamilton Anxiety Rating Scale (HAM-A) [119]		
Quality of Life	Heinrich Carpenter Quality of Life Scale [120]		

Table 9

Cognitive Test Batteries and Questionnaires

Test	Cognitive Domains	Administration Time	Pros/Cons
Neuropsychological Tests			
Measurement and Treatment to Improve Cognition in Schizophrenia (MATRICS) [99]	Speed of processing	60 min	Interview-based rating scale Strong correlation with functional outcome
	Attention/vigilance		
	Working memory		
	Verbal learning		
	Visual learning		
	Reasoning/problem solving		
	Social cognition		
Clinical Global Impression of Cognition in Schizophrenia (CGI-CogS) [104]	Speed of processing	30 min	Interview-based rating scale Strong correlation with functional outcome
	Attention/vigilance		
	Working memory		
	Verbal learning		
	Visual learning		
	Reasoning/problem solving		
	Social cognition		
CogState Schizophrenia Battery [105, 106]	Speed of processing	35 min	Valid measurement of MATRICS cognitive domains Designed for clinical trial use
	Attention/vigilance		
	Working memory		
	Verbal learning		
	Visual learning		
	Reasoning/problem solving		
	Social cognition		
CogState 12-Minute Battery [107]	Executive function	12 min	Designed for clinical trial use
	Psychomotor function		
	Visual attention		
	Visual learning		

Test	Cognitive Domains	Administration Time	Pros/Cons
Schizophrenia Cognition Rating Scale (SCoRS) [108]	Speed of processing	12–14 min for each of 3 interviews (patient, informant, and interviewer)	Excellent correlations with performance and functional outcomes Appropriate for clinical use
	Attention/vigilance		
	Working memory		
	Verbal learning		
	Visual learning		
	Reasoning/problem solving		
Repeatable Battery for Assessment of Neuropsychological Status (RBANS) [109, 110]	Immediate memory	25–45 min	Lacks measures of motor, executive, and working memory Appropriate for clinical use
	Visuospatial/constructional ability		
	Language		
	Attention		
	Delayed memory		
Brief Assessment of Cognition in Schizophrenia (BACS) [111]	Reasoning/problem solving	<35 min	Appropriate for clinical use
	Verbal fluency		
	Attention		
	Verbal memory		
	Working memory		
	Motor speed		
Brief Cognitive Assessment Tool for Schizophrenia (B-CATS) [112]	Attention	10–11 min	Appropriate for clinical setting
	Language		
	Processing speed		
5-minute Digit Symbol Coding Task [113]	Processing speed	5 min	Limited to 1 domain Appropriate for clinical setting
Questionnaires/Interviews			
Behavior Rating Inventory of Executive Functioning (BRIEF) [114]	Behavioral Regulation Index (BRI): Inhibit, Shift, and Emotional Regulation subdomains.	10-15 minutes (as per authors)	Scale consists of a 86 questions real-world task related Parent Form and 86 questions Teacher Form. Questions are answered as “never, “sometimes”, “often”.
	Metacognition Index (MCI): Initiate, Working, Memory, Plan/Organize, Organization of Materials, and Monitor subdomains.		
	Global Executive Composite (GEC) = BRI + MCI		
New York Assessment of Adverse Cognitive Effects of Neuropsychiatric Treatment (NY-AACENT) [115]	Working memory	5-7 minutes	Clinician interview integrates informant data, patient self-report (separate forms) and indirect assessment based on real-

Test	Cognitive Domains	Administration Time	Pros/Cons
	Attention/Vigilance		life observations/impact. 7 probes/items rated “not present”, “a little bit bothersome”, “somewhat bothersome”, “quite bothersome”, “very bothersome” (Note: validation underway). Appropriate for clinical use
	Verbal Learning/Memory		
	Visual Learning/Memory		
	Reasoning & Problem Solving		
	Speed of Processing		
	Social Cognition		