Protocol of the study:
Early improvement for predicting response in schizophrenia: a diagnostic test review

Abstract

Background
Schizophrenia is often a chronic and disabling psychiatric disorder. The degree of suffering and disability is considerable with 80-90% not working and up to 10% dying by suicide. The main reason for this poor psychosocial outcome is the high rate of treatment resistance. Thus, identifying the optimum treatment of this disorder is crucial.
Objectives
Antipsychotic drugs are the core treatment for schizophrenia. Our main goal is to provide a diagnostic test review on the question whether early improvement to antipsychotic drugs (at least 20% PANSS total score reduction at two weeks) can be used as a test for subsequent response and remission in acute schizophrenia.
Search methods
We will carry out a comprehensive literature search of electronic databases (EMBASE, MEDLINE, PubMed, BIOSIS, Cinahl, PsychInf, Cochrane Library), with terms combining antipsychotic drugs, schizophrenia and prediction of response: [(schizophreni* or schizoaff* or schizo-aff*) AND (antipsychoti* or neurolepti*) AND (early improvement or early non-respon* or early respon* or prediction* or diagnostic test)]. We will search additionally in clinicaltrials.gov, contact study authors and pharmaceutical companies for further trials. We will consult a search specialist (Samantha Roberts) to ensure the highest standards in our search methods.
Selection criteria
Population (of patients): People with schizophrenia or related disorders (schizoaffective-, or schizophreniform disorder)
Intervention: Monotherapy with an antipsychotic drug
Outcomes: Sensitivity and specificity for each study based on early improvement, summary ROC analysis, positive and negative predictive values
Design of primary studies: clinical drug trials irrespective of the design (RCTs, case control studies, case series)
Data collection and analysis
All data will be extracted independently by at least two reviewers. Doubts will be resolved in a discussion with a third reviewer. Remaining discrepancies will be resolved by a written request to the first author. Data entry will be checked with the double data entry function of RevMan. We will analyse the sensitivity and specificity of early improvement (primarily defined as at least 20% PANSS reduction after two weeks) to predict response at follow-up (primarily defined as at least 50% PANSS reduction after six weeks). We will present the data in a summary ROC-plot/space, and we will calculate positive and negative predictive values. Heterogeneity will be addressed by visual inspection of the forest plots, subgroup analyses and meta-regression. We will also perform quality assessment using the QUADAS criteria.

Background

Prediction of response to antipsychotic treatment is complex and limited. A number of factors have been identified as possible predictors of subsequent response to antipsychotics, with early improvement appearing as one of the predominant. Despite strong evidence to the contrary (1, 2), the theory of delay between initiation of treatment and response still holds and orientates most recent clinical guidelines for the treatment of schizophrenia. NICE guidelines (3) recommend extending the duration of treatment with the initial medication at optimal dosage for at least 4 to 6 weeks whereas WFSBP guidelines (4) 4 to 10 weeks before switching to another antipsychotic. With regard to all the above, adequacy of early improvement to differentiate patients with subsequent response to an antipsychotic from those who will not respond will be assessed.

Target condition being diagnosed

Schizophrenia is among the most expensive illnesses in Germany (5). It is also among the seven most frequent causes listed by the WHO for loss of years of life due to disability (World Health Organisation, 2001) (6). It thus leads popular diseases such as diabetes, heart disease or cancer. Despite newly advanced treatment methods, schizophrenia still presents a tremendous burden to patients and their families: 80-90 % of the schizophrenic patients do not work (7) and more than 10 % commit suicide (8). The main reason for this poor psychosocial outcome is the high rate of treatment resistance. The American and the German national treatment guidelines state that 30% of patients do not respond to an antipsychotic drug trial (9, 10). It has also been reported that, in many RCTs, as many as 70% of the participants are not even minimally improved (11). Thus, identifying the optimum treatment of this disorder is crucial.

Rationale

The assumption of delayed onset of antipsychotic drug action for several weeks is the reason why international treatment guidelines recommend waiting for at least 4-6 and some even up to 10 weeks before switching an antipsychotic due to non-response (4, 9, 10). However, two recent meta-analyses, one by our group, have clearly rejected the delay of antipsychotic drug action hypothesis (1, 2). Agid et al 2003 (~8000 participants) found that in a 4-week course the greatest symptom reduction occurred within the first week and got continuously smaller after this.

These results were corrected for possible placebo effects and they were found in both overall and positive symptoms. Leucht et al (2) replicated Agid's findings in a large original patient database of 1708 participants from antipsychotic drug trials. Again, the greatest symptom reduction occurred within the first week and the additional improvement got consistently smaller after this. Furthermore, the additional gain between four weeks and one year was small, excluding the possibility that there is a large improvement in the very long-term.

These key-meta-analyses suggested that one could possibly predict very early (already 2 weeks after the initiation of treatment) whether the chosen antipsychotic would finally be effective or not. In addition, a number of individual studies showed that early improvement of symptoms, usually defined as at least 20% reduction of the Positive and Negative Syndrome Scale (PANSS) (12) at 2 weeks, predicts later full-response with good sensitivity, specificity positive and negative predictive value (13-17).

However, diagnostic test characteristics have never been systematically reviewed and evaluated. This would be the aim of this diagnostic test review applying the methods of the Cochrane Collaboration Diagnostic Test Review Group (18). Different cut-offs will be examined in order to identify the optimal one since different studies have found similar but not identical cut-offs in order to predict later response.

Furthermore, a meta-analysis of the available studies will provide a better estimate of the specificity, sensitivity, positive and negative predictive power of the test. The results of this meta-analysis will help to decide whether the test is good enough to be implemented in treatment; this is currently not the case yet. If the results are good enough, this would certainly be clinically feasible, because it would be sufficient to apply the Positive and Negative Syndrome Scale (PANSS) (12) at baseline and at two weeks, calculate the percentage PANSS total score reduction achieved and decide whether the patient is likely to respond or not. In the latter case, the antipsychotic should rather be switched

in order not to lose time, reduce the suffering of patients and minimize unnecessary hospitalisation costs.
The expected results could have major implications on treatment guidelines.

Objectives

The outcome in a diagnostic test review can be defined as the sensitivity and specificity of the test. In our review, this is the sensitivity and specificity of the cut-off 'at least 20% PANSS improvement at two weeks' as a definition of early improvement. We will extract the necessary numbers for the two-by-two tables to calculate these parameters together with their respective 95% confidence interval for each individual study. Then, an average summary value of sensitivity and specificity will be computed. We will primarily attempt to calculate these numbers based on the cut-off 'at least 20% PANSS reduction at two weeks' and, for that reason, we will send a request for further information to the authors. However, different cut-offs, ranging for at least above 0% to 50% reduction, will also be examined.

Secondary objectives

Investigation of sources of heterogeneity

In diagnostic reviews, considerable variability in test accuracy between studies is usually observed; this is greater than one would expect from within study sampling error alone and is reflected in the specifications of the bivariate model (19) which allows for random study effects. Therefore, we will assess the influence of sources of heterogeneity on the diagnostic accuracy of tests performed. The feasibility of such analyses will obviously be influenced by the number of available studies in each subgroup. Despite possible limitations, we *a priori* define the following subgroups:
1. First episode versus multiple episode patients: the rational is that first-episode patients generally respond better to antipsychotic drugs which may change the test results.
2. Patients in randomised controlled trials versus naturalistic cohort studies
3. Patients diagnosed by operationalised criteria such as ICD-10 or DSM-IV versus clinical diagnoses.
If any currently unforeseeable important subgroup analyses should come up during the review process, these will be clearly described as post-hoc. Also, if a sufficient number of studies with moderator data will be available, heterogeneity will also be addressed with meta-regression using the potential effect moderators as covariates.

Methods

Index tests

The index test will be the early improvement of symptoms defined as at least 20% reduction of the Positive and Negative Syndrome Scale (PANSS) (12) baseline score at two weeks. We have shown that this cut-off means minimal improvement according to the Clinical Global Impression (20) of the raters (21, 22).
The PANSS rates the overall symptoms of schizophrenia by 30 items, each of which can be defined on a seven-point scoring system varying from one - absent - to seven extreme - and which can be added to form a total score. A low score indicates lesser severity. It is a well-known diagnostic and therapeutic monitoring instrument that is widely used in clinical routine and in antipsychotic drug trials on schizophrenia. Percentage reduction of the PANSS total score is simply calculated by the formula Percentage PANSS reduction at two weeks = (PANSSb PANSSw2) * 100 / (PANSSb 30), where PANSSb = PANSS total score at baseline,
PANSSw2 = PANSS total score at two weeks, and 30 is the minimum score on the 1-7 scoring system. Studies that used the Brief Psychiatric Rating Scale (BPRS) (23) instead of the PANSS will also be used, because both scales are highly correlated (24). The main reason is that all 18 BPRS items are included in the PANSS, as well.
In most of the studies identified in our preliminary search, at least 20% reduction of the PANSS from baseline was the optimum test for later response (14-16). If the original authors did not use this exact cut-off, but rather a slightly different one e.g. at least 25% PANSS, we will ask the authors to send us the results based on at least 20% PANSS reduction. Furthermore, we will also examine the results of other cut-offs such as at least 25% and at least 30% PANSS reduction. Please note that most of the relevant studies were recent, that we know most authors personally and that we have

already sent requests to the first authors of the publications listed above (13-17) who have expressed their general willingness to contribute. Therefore, we are confident that we will be able to obtain any missing data.

Comparator tests

We will not be using a comparator test in this review.

Target conditions

Schizophrenia.

Reference standards

Response at follow-up (reference tests):

In our context, the reference standard will be subsequent response to antipsychotics, primarily defined as at least 50% reduction of the PANSS/BPRS. In two independent studies, we have shown that this definition is clinically meaningful, equalling to much improved from the perspective of the raters using the equipercentile linking method (21, 22). Secondary definitions of subsequent response will be at least 20% reduction of PANSS/BPRS and remission as defined by Andreasen et al. (25) and van Os et al. (26). As mentioned already, at least 20% reduction of the Positive and Negative Syndrome Scale

(PANSS) (12) means minimal improvement according to the Clinical Global Impression (20) of the raters (21, 22). Regarding the definition by Andreasen, criteria for remission are fulfilled if eight core items of the PANSS are not rated higher than mildly present. Separate (stratified) analyses will be carried out for these three different reference standards, and/or data will be clearly presented separately. The exact definition of a positive outcome of the reference standard in every study will be also clearly described. If possible, above data will be also combined.

Search methods for identification of studies

Electronic searches

We will search in electronic databases (EMBASE, MEDLINE, BIOSIS, PsychLit, PsychInf, Cochrane Library), supplemented by the regular hand searching of relevant journals and numerous conference proceedings. The search strategy will combine terms for antipsychotic drugs and schizophrenia with terms for prediction of response to treatment: [(schizophreni* or schizoaff* or schizo-aff*) AND (antipsychoti* or neurolepti*) AND (early improvement or early non-respon* or early respon* or prediction* or diagnostic test)]. We will additionally search in clinicaltrials.gov to identify further relevant trials. The exact search terms will be detailed with the search coordinator of the Cochrane Schizophrenia Group (Samantha Roberts) which has agreed to collaborate in the project.

Searching other resources

1. Reference searching

We will inspect the references of all identified studies for more trials.

2. Searching previous reviews

We will search the reference lists of previous narrative reviews on the topic.

3. Personal contact

We will contact the first author of each included study for missing information and for the existence of further studies.

4. Drug companies

We will contact the manufacturers of antipsychotic drugs and ask them for further relevant studies and for missing information on any identified studies.

5. Hand searching

We will additionally hand search of major conference reports.

Selection of studies

Two reviewers will independently inspect all abstracts identified by the searches. Disagreement will be resolved by discussion and, if necessary, the full article will be acquired for further inspection. Once the full articles will be obtained, at least two reviewers will independently decide whether the studies meet the review criteria. If disagreement cannot be resolved by discussion, we will seek further information from the study authors.

Data extraction and management

We will follow the available guidelines provided in the *Cochrane Diagnostic Reviewers Handbook* (DTA Handbook 2011). Two reviewers will independently extract data from *all* selected trials. We will extract the diagnostic two-by-two table (true positive, false positive, true negative and false negative index test results) from the publications with respective 95% confidence intervals, or if not available, reconstruct the two-by-two table using information on relevant parameters (sensitivity, specificity or predictive values). Eligible studies for which the diagnostic two-by-two table could not be reconstructed will be presented in the review, but not included in the quantitative analyses. Disagreements will be resolved by discussion and, if necessary, by consulting a third review author. If still no consensus can be obtained, we will contact the study authors to resolve the dilemma.
In addition to the values needed for the two-by-two tables, our standardised extraction sheets will include characteristics of participants, index tests and reference standards, and study methods.
Characteristics of participants: inclusion and exclusion criteria; enrolment (consecutive or non-consecutive); number of subjects (including number eligible for the study, number enrolled in the study, number receiving index test and reference standard, number for whom results are reported in the two-by-two table, reasons for withdrawal); sex; age; personal psychiatric history (operationalised criteria versus clinical diagnosis, age of diagnosis, duration of illness, number of previous hospitalisations, baseline severity, etc.); family psychiatric history; and substance abuse.
Test characteristics: type and version of the scale used as index test and/or reference standard; experience; expertise and blindness of the assessors; time (weeks) between baseline, index test and reference standard; and cut-off points for defining early improvement and response. Positivity thresholds (interpretations of positive results) may vary across studies, and some studies may present diagnostic performance of an index test at several different cut-off points. We will extract all data presented in the publications of the studies and we will also try to contact study authors for further information. We will define which positivity thresholds were determined a priori and which were driven by the data post hoc.
Characteristics of study methods: study design (treatment or observational, randomized or not, case series, ad hoc or post hoc design etc.); duration; setting; sponsorship; treatment (type of drug, need for titration or not, fixed or flexible schedule, dosage, co-medication, route of administration for co-medication); and quality assessment (see section on assessment of methodological quality).

Assessment of methodological quality

Methodological quality will be assessed by two independent authors using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) instrument (27, 28) . QUADAS consists of 14 items that refer to internal validity (for example, blind assessment of index and reference test, or avoidance of verification bias). We will not exclude studies based on this assessment, but it will help to understand and describe the overall quality of the available data.
The tool consists of 14 items which can be answered with yes, no, unclear:
1. Was the spectrum of patients representative of the patients who will receive the test in practice?
2. Were selection criteria clearly described?
3. Is the reference standard likely to correctly classify the target condition?
4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?
5. Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?
6. Did patients receive the same reference standard regardless of the index test results?
7. Was the reference standard independent of the index test?
8. Was the execution of the index test described in sufficient detail to permit its replication?
9. Was the execution of the reference standard described in sufficient detail to permit its replication?
10. Were the index test results interpreted without knowledge of the results of the reference standard?
11. Were the reference standard results interpreted without knowledge of the results of the index test?

12. Were the same clinical data available when the test results were interpreted as would be available when the test is used inpractice?
13. Were uninterpretable/intermediate test results reported?
14. Were withdrawals from the study explained?
We have added two items regarding the prior or posterior to the start of the study establishment of cut-off values and the subtraction of 30 points from PANSS or 18 points from BPRS before the calculation of the relative change in PANSS or BPRS. We will classify each item as 'yes' (adequately addressed), 'no' (inadequately addressed), or 'unclear'. Disagreements will be resolved by discussion and, if necessary, by consulting a third review author. We will not exclude studies based on this assessment, but we will evaluate the overall quality of the available data.
We will not apply weights to the different items of the checklist, and will not use a summary score to incorporate studies with certain levels of quality in the analysis. We will explore the influence of negative scores on important items using subgroup analyses or meta-regression analyses (see below).

Statistical analysis and data synthesis

The two key and commonly reported parameters of diagnostic test accuracy are sensitivity and specificity. Because a trade-off may exist between these two parameters, they should be analysed jointly. Sensitivities and specificities for each index test with 95% confidence intervals will be presented in forest plots. In addition, a scatterplot of study-specific estimates of sensitivity and 1-specificity will be used to display data in Receiver Operating Characteristic (ROC) space in Review Manager. For the meta-analysis of diagnostic accuracy measures, two models are available: the bivariate model (19) and the mathematically equivalent hierarchical summary ROC (HSROC) model (29). These models both take into account the within study variation and the between study variation. Although both models will give the same results when no covariates are added, their focus may be slightly different: the bivariate ROC model focuses on estimating a summary estimate of sensitivity and specificity (and thus focuses at one operating point), whereas the HSROC model focuses on the summary ROC curve as a whole (and thus not on one operating point but on the global accuracy over a range of operating points). For policy making decisions and calculations of (financial, psychological and societal) costs, summary sensitivity and specificity are more useful. Thus, we will estimate the diagnostic accuracy for early identification of patients who will probably respond or not to antipsychotic treatment by analysing the results of the included studies separately for each predefined cut-off point. On the other hand, diagnostic tests may report different cut-off values for early improvement. If this is indeed the case, and the quantitative tests are all done at different cut-off values, we will use the HSROC model.
We will summarise the findings of the review in a 'Summary of results' table. This table will include, if possible, a summary estimate of either the diagnostic odds ratio (DOR) or another description of the HSROC curve (when using the HSROC model) or sensitivity and specificity (when using the bivariate model) for relevant subgroups of studies. We will furthermore provide an explanation of these results plus any potential impact for practice, as well as a comment on the quality of the evidence we provide. The presentation of this summary table will make diagnostic information more accessible to healthcare providers and other end users. As predictive values are particularly relevant for policy makers, we will calculate these measures from the pooled estimates obtained from the models. The exact mode of calculation will depend on whether there are a limited number of operating points per test, or not.

Investigations of heterogeneity

Heterogeneity will be investigated initially through visual examination of forest plots of sensitivities and specificities and through visual examination of the ROC plot of the raw data. It will be formally assessed by examining differences in diagnostic accuracy between subgroups of studies or, if possible, patients. Although both meta-analytic models can be extended to include a covariate into the models, again their interpretation will vary. The HSROC model allows a statistical assessment of the evidence for an association between the position and shape of the SROC curve and potential sources of heterogeneity, while the bivariate model allows a statistical assessment of the evidence for an association between the summary sensitivity and specificity and potential sources of heterogeneity.

Several factors (next to variability in the positivity threshold) may contribute to heterogeneity in diagnostic performance across studies. Sources of heterogeneity that we will assess will be based on data extracted such as age, sex, psychiatric history, baseline severity, treatment and study design. Where there is sufficient data, we will include these features as covariates in the models.

Sensitivity analyses

Furthermore, in order to prove that the findings from our systematic review are not dependent on arbitrary or unclear decisions, we will perform a sensitivity analysis. The meta-analysis will be repeated, substituting alternative decisions of ranges of values for decisions that were arbitrary or unclear. For example, if the eligibility of some studies in the meta-analysis is dubious because they do not contain full details, sensitivity analysis may involve undertaking the meta-analysis twice: first including all studies, and second, only including those that are definitely known to be eligible. We define *a priori* that we will conduct a sensitivity analysis excluding trials with low quality according to our assessment with the QUADAS instrument (30). Again, if other sensitivity analyses should be made, these will be clearly described as post-hoc.

Assessment of reporting bias

Statistical tests detect funnel plot asymmetry in general rather than publication bias specifically. Tests for funnel plot asymmetry designed primarily for use in randomized trials should not be used with diagnostic studies. Applying such tests for funnel plot asymmetry in systematic reviews of diagnostic test accuracy is likely to result in publication bias being incorrectly indicated by the test far too often, i.e. a type I error rate that is too high.

A more appropriate method for detecting funnel plot asymmetry in reviews of diagnostic studies has been developed by Deeks et al. 2005 (31). It tests for association between the ln-transformed diagnostic odds ratio (OR) and the effective sample size, a simple function of the number of responders and non-responders. However, the extent and determinants of publication bias in diagnostic studies is a point of further research.

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Table S1. Description of included studies

Angehelescu 2011(1-3)	Methods	Double-blind RCT Duration: 12 weeks (response was assessed at 6th week for our analysis) ITT and OC analysis
	Participants	Schizophrenia (DSM-IV), acutely ill for less than 6 months, PANSS total score between 60 and 120 Setting: inpatients for 2 weeks, later discharge was possible N: 93 Sex: 49 males, 44 females Age: 38.6±10.8 years
	Interventions	Olanzapine 20mg/day, fixed dosing schedule (other groups not included in our analysis: JNJ-37822681 20mg/d, JNJ-37822681 40mg/d, JNJ-37822681 60mg/d, and placebo)
	Rating Scale	PANSS
	Sponsor	Janssen Research and Development
Ascher-Svanum 2008(4)	Methods	Open-label RCT Duration: 1 year (response was assessed at 8th week for our analysis) OC analysis
	Participants	Schizophrenia, schizoaffective disorder, or schizophreniform disorder (DSM-IV), BPRS total score (0-6) ≥18; patients required a medication change due to inefficacy or intolerability change (vast majority met symptom criteria) Setting: 95% outpatients N: 443 Sex: 274 males, 169 female Age: 43.6±12 years
	Interventions	Olanzapine 5-20mg/d, risperidone 4-16mg/d andor typical antipsychotics of physician's choice (e.g. haloperidol 11±9.5mg/d and perphenazine 14.2±10.6mg/d), flexible dosing schedule
	Rating scale	PANSS
	Sponsor	Eli Lilly Company
Beasley 1996a(5)	Methods	Double-blind RCT Duration: 6 weeks ITT and OC analysis
	Participants	Schizophrenia (DSM-III-R), residual type excluded, BPRS total score (0-6) ≥24 & CGI-S score≥4 Setting: inpatients for 2 weeks, later discharge was possible N: 50 Sex: 37 males, 13 female Age: 38.8±10.2 years
	Interventions	Olanzapine 10 mg/day, fixed dosing schedule (olanzapine 1.0 mg/d and placebo were excluded)
	Rating scale	PANSS
	Sponsor	Eli Lilly Company
Beasley 1996b(6)	Methods	Double-blind RCT Duration: 6 weeks (possible 46-week double-blind extension for responders) ITT and OC analysis

	Participants	Schizophrenia (DSM-III-R), acutely ill, BPRS total score (0-6) ≥24 Setting: inpatients for 2 weeks, later discharge was possible N: 202 Sex: 172 males, 30 female Age: 36.2±9.7 years
	Interventions	Olanzapine 10±2.5 mg/day, olanzapine 15±2.5 mg/day or haloperidol 15±5.0 mg/day (olanzapine 5±2.5 mg/d and placebo groups were excluded)
	Rating scale	BPRS
	Sponsor	Eli Lilly Company
Beasley 1997(7)	Methods	Double-blind RCT Duration: 6 weeks (possible 46-week double-blind extension for responders) ITT and OC analysis
	Participants	Schizophrenia (DSM-III-R), acutely ill, BPRS total score (0-6) ≥24 & CGI-S score≥4 Setting: inpatients for 2 weeks, later discharge was possible N: 255 Sex: 159 males, 96 females Age: 35.8±10.8 years
	Interventions	Olanzapine 10±2.5 mg/day, olanzapine 15±2.5 mg/day, or haloperidol 15±5.0 mg/day (olanzapine 5±2.5 mg/day and olanzapine 1.0 mg/d excluded)
	Rating scale	PANSS
	Sponsor	Eli Lilly Company
Breier 2005(8)	Methods	Double-blind RCT Duration: 28 weeks (response was assessed at 6th week for our analysis) ITT and OC analysis
	Participants	Schizophrenia (DSM-IV), acutely ill, BPRS total score (1-7) ≥42 & at least one positive symptom item of the PANSS & CGI-S score≥4 Setting: in- and outpatients N: 548 Sex: 352 males, 196 females Age: 39.2±11.9 years
	Interventions	Olanzapine 10–20 mg/day or ziprasidone 80–160 mg/day, flexible dosing schedule
	Rating scale	PANSS
	Sponsor	Eli Lilly Company
Carriere 2000(9)	Methods	Double-blind RCT Duration: 16 weeks (response was assessed at 4th week for our analysis) ITT and OC analysis
	Participants	Paranoid schizophrenia or schizophreniform disorder (DSM-IV) Setting: inpatients for 2 weeks, later discharge was possible N: 202 Sex: 136 males, 66 females Age: 31±8.6 years
	Interventions	Amisulpride (400–1200 mg/d) or haloperidol (10–30 mg/d), flexible dosing schedule

	Rating scale	BPRS
	Sponsor	Sanofi Synthélabo
Colonna 2000(10)	Methods	Open RCT Duration: 1 year (response was assessed at 4th week for our analysis) ITT and OC analysis
	Participants	Sub-chronic or chronic schizophrenia with acute exacerbation (paranoid, disorganised or undifferentiated) (DSM-III-R), at least 2 of the 4 BPRS positive items≥4 Setting: outpatients (could be hospitalised in the initial phase) N: 488 Sex: 327 males, 161 females Age: 37.5±11.1 years
	Interventions	Amisulpride 200-800 mg/day or haloperidol 5-20 mg/day, flexible dosing schedule
	Rating scale	BPRS
	Sponsor	Sanofi Synthélabo
Correll 2003(11)	Methods	Observational, open-label study (lead-in phase) Duration: 8 weeks (response was assessed at 4th week of the lead-in phase for our analysis) ITT and OC analysis
	Participants	Schizophrenia, schizoaffective disorder, or schizophreniform disorder (DSM-III-R), acutely ill, moderate or worse on at least one of the four BPRS psychotic symptom items Setting: inpatients N: 131 (151 patients entered the original study from Kinon(12)) Sex: 82 males, 49 females Age: 29.4±6.6 years
	Interventions	Fluphenazine 20mg/d, fixed dosing schedule
	Rating scale	BPRS
	Sponsor	No
Correll 2013(13)	Methods	Double-blind RCT Duration: 6 weeks ITT analysis
	Participants	Schizophrenia (DSM-IV), adolescents 13 to 17 years old Setting: outpatients, partial hospitalized, or fully inpatients N: 202 Sex: 110 males, 92 females Age: 15.5±1.4 years
	Interventions	Aripiprazole 10mg/d or 30 mg/d, fixed dosing schedule (placebo group was excluded)
	Rating scale	PANSS
	Sponsor	Otsuka Pharmaceutical Co.
Correll 2014(14)	Methods	Double blind RCT Duration: 6 weeks ITT analysis
	Participants	Schizophrenia (DSM-IV-TR), adolescents 13 to 17 years old Setting: inpatients and outpatients N: 72 Sex: 51 males, 21 females Age: 16.1±1.3
	Interventions	Olanzapine 2.5-20.0 mg/day, flexible dosing schedule (placebo

		group was excluded)
	Rating scale	BPRS-C
	Sponsor	Eli Lilly Company
Giegling 2010(15, 16)	Methods	Naturalistic trial Duration: 4 weeks ITT and OC analysis
	Participants	Schizophrenia (DSM-III-R), acutely ill, first episode Setting: inpatients N: 101 Sex: 54 males, 47 females Age: 34.28±11.29
	Interventions	Haloperidol, flexible dosing schedule without any dose limitation
	Rating scale	PANSS
	Sponsor	No
Hatta 2003(17)	Methods	Case-control study Duration: 8 weeks ITT and OC analysis
	Participants	Schizophrenia, schizotypal and delusional disorders (ICD-10), at least moderate on at least one of the PANSS positive symptom items, all female first-episode patients Setting: inpatients (newly admitted) N: 13 Sex: 0 males, 13 females Age: 34.2±12.2
	Interventions	Risperidone 1-12 mg/day, flexible dosing schedule
	Rating scale	PANSS
	Sponsor	No
HERA041004(18, 19)	Methods	Double-blind RCT Duration: 6 weeks ITT and OC analysis
	Participants	Schizophrenia; disorganized, paranoid, catatonic or undifferentiated subtypes (DSM-IV), acute exacerbation; CGI-S≥4&PANSS≥60 Setting: inpatients and outpatients N: 114 Sex: 80 males, 34 females Age: 40.8±10.7
	Interventions	Asenapine 5mg BID or risperidone 3mg BID, fixed dosing schedule (placebo group excluded)
	Rating scale	PANSS
	Sponsor	Merck &Co, Inc (Organon Bioscience)
HERA041021(18)	Methods	Double-blind RCT Duration: 6 weeks ITT and OC analysis
	Participants	Schizophrenia, acute exacerbation Setting: inpatients and outpatients N: 293 Sex: 218 males, 75 females Age: 34.2±12.2
	Interventions	Asenapine 5mg BID or 10mg BID or olanzapine 15mg QD, fixed dosing schedule (placebo group excluded)

	Rating scale	PANSS
	Sponsor	Merck &Co, Inc (Organon Bioscience)
HERA041023(18, 20)	Methods	Double-blind RCT Duration: 6 weeks ITT and OC analysis
	Participants	Schizophrenia(DSM-IV-TR), acute exacerbation, CGI-S≥4&PANSS≥60 Setting: inpatients and outpatients N: 326 Sex: 200 males, 126 females Age: 38.1±11.4
	Interventions	Asenapine 5mg BID or 10mg BID or haloperidol 4mg BID, fixed dosing schedule (placebo group excluded)
	Rating scale	PANSS
	Sponsor	Merck &Co, Inc (Organon Bioscience)
Kayo 2012(21)	Methods	Open RCT to FGAs or SGAs; the choice of drug was left to the discretion of treating psychiatrist Duration: 8-12 weeks (switch after 4-6 weeks in case of non-response; thus, response was assessed at 4th week for our analysis) ITT and OC analysis
	Participants	Schizophrenia or schizoaffective disorder (DSM-IV-TR), exacerbation of recent onset schizophrenia, PANSS total score≥ 60 & CGI-S score≥ 4 & duration of illness<5 years Setting: outpatients N: 20 Sex: 10 males, 10 females Age: 30.05±8.06
	Interventions	FGAs: Haloperidol 5-10 mg/d, chlorpromazine 25-800 mg/d or trifluoperazine 5-10 mg/d SGAs: Aripiprazole 15-30 mg/d, olanzapine, 5-20 mg/d, quetiapine 25 - 800 mg/d, risperidone 1-6 mg/d, ziprasidone, 80-160 mg/d, flexible dosing schedule
	Rating scale	PANSS
	Sponsor	No
Keefe 2006(22)	Methods	Double-blind RCT Duration: 52 weeks (response was assessed at 6th week for our analysis) ITT and OC analysis
	Participants	Schizophrenia or schizoaffective disorder (DSM-IV), at least 2 positive items on the PANSS≥4 &BPRS (0-6)≥18 Setting: inpatients and outpatients N: 414 Sex: 295 males, 119 females Age: 39.1±8.1
	Interventions	Olanzapine 5-20 mg/d, risperidone 2-10 mg/d, or haloperidol 2-19 mg/d, flexible dosing schedule
	Rating scale	PANSS
	Sponsor	Eli Lilly Company
Kinon 2006(23)	Methods	Double-blind RCT Duration: 6 months (response was assessed at 6th week for our analysis)

		ITT and OC analysis
	Participants	Schizophrenia or schizoaffective disorder (DSM-IV), prominent negative symptoms & social and functional impairment Setting: outpatients N: 346 Sex: 228 males, 118 females Age: 41.05±9.6
	Interventions	Olanzapine 10-20 mg/d or quetiapine 300-700mg/d, flexible dosing schedule
	Rating scale	PANSS
	Sponsor	Eli Lilly Company
Kinon 2010(24)	Methods	Two study periods: 1st All patients treated with risperidone for 2 weeks 2nd Double-blind RCT; early responders to risperidone continued with risperidone, whereas early non-responders were randomized to risperidone or olanzapine for 10 weeks (patients switching to olanzapine group were excluded from our analysis) Duration: 12 weeks ITT analysis
	Participants	Schizophrenia, schizoaffective disorder, or schizophreniform disorder (DSM-IV) Setting: inpatients and outpatients N: 346 Sex: 322 males, 200 females (referring to the whole sample) Age: 41.85±11.04
	Interventions	Risperidone 2-6 mg/d, flexible dosing schedule (patients switching to olanzapine group were excluded)
	Rating scale	PANSS
	Sponsor	Eli Lilly Company
Lambert 2009(25)	Methods	Open-label, observational trial Duration: 12 weeks (response was assessed at 4th week for our analysis) ITT and OC analysis
	Participants	Schizophrenia (ICD-10), severe level of impairment Setting: outpatients N: 528 Sex: 266 males, 262 females Age: 41.3±12.2
	Interventions	Amisulpride 100-1200 mg/d, flexible dosing schedule
	Rating scale	PANSS (only sum of positive and negative items)
	Sponsor	Sanofi-Aventis
Lieberman 2003(26)	Methods	Double-blind RCT Duration: 104 weeks (response was assessed at 6th week for our analysis) ITT and OC analysis
	Participants	Schizophrenia, schizophreniform disorder, or schizoaffective disorder (DSM-IV), first episode, at least two PANSS psychosis items≥4 or one≥5 & CGI-S≥4 Setting: inpatients, emergency patients and outpatients N: 263

		Sex: 215 males, 48 females Age: 23.8±4.8
	Interventions	Olanzapine 5–10 mg/d or haloperidol 2–6 mg/d (for the initial 6 weeks assessed), flexible dosing schedule
	Rating scale	PANSS
	Sponsor	Eli Lilly Company
Lin 2012(27, 28)	Methods	Naturalistic, open-label trial Duration: 4 weeks OC analysis
	Participants	Schizophrenia (DSM-IV), acute exacerbation, newly hospitalized patients, moderate or worse on at least 1 of the 4 BPRS psychotic symptom items Setting: inpatients N: 100 Sex: 54 males, 46 females Age: 37.3±9.1
	Interventions	Zotepine 150mg/d, fixed dosing schedule
	Rating scale	BPRS
	Sponsor	No
Moller 1997(29)	Methods	Double-blind RCT Duration: 6 weeks ITT and OC analysis
	Participants	Schizophrenia, chronic or subchronic, paranoid, disorganised or undifferentiated (DSM-III-R), four core BPRS productive symptoms≥12 with at least 2 of these items≥4 Setting: inpatients for 4 weeks, later discharge was possible N: 191 Sex: 119 males, 72 females Age: 36±11
	Interventions	Amisulpride 800 mg/d or haloperidol 20 mg/d, fixed dosing schedule
	Rating scale	BPRS
	Sponsor	Sanofi Synthélabo
Park 2014(30)	Methods	Open-label, single-arm clinical trial Duration: 6 weeks ITT analysis
	Participants	Schizophrenia, schizophreniform disorder, schizoaffective disorder, or psychotic disorder not otherwise specified (DSM-IV), first-episode, at least two PANSS psychosis items≥4 or one≥5 & no lifetime antipsychotic exposure of 2 consecutive weeks Setting: inpatients N: 59 Sex: 27 males, 32 females Age: 30±10.8
	Interventions	Aripiprazole 5-30 mg/d, flexible dosing schedule
	Rating scale	PANSS
	Sponsor	Otsuka Pharmaceutical Company
Pelayo-Teran 2010(31)	Methods	Open RCT Duration: 3 year-study (only results from the initial 6-week acute phase were included in our analysis) ITT analysis

	Participants	Brief psychotic disorder, schizophreniform disorder, schizophrenia, schizoaffective disorder, schizotypal personality disorder or psychosis non otherwise specified (DSM-IV), first episode of psychosis (in our analysis only patients with schizophrenia, schizoaffective or schizophreniform disorder were included) Setting: inpatients and outpatients N: 151 Sex: 94 males, 57 females Age: 26.8±7.5
	Interventions	Olanzapine 5–20 mg/d, risperidone 3–6 mg/d or haloperidol 3–9 mg/d, flexible dosing schedule
	Rating scale	BPRS
	Sponsor	No
Peuskens 1999(32)	Methods	Double-blind RCT Duration: 8 weeks (response was assessed at 6th week for our analysis) ITT and OC analysis
	Participants	Schizophrenia, paranoid, disorganized or undifferentiated type (DSM-IV), BPRS≥36 & four BPRS items from psychosis cluster≥12 with at least 2 of these items≥4 Setting: inpatients and outpatients N: 228 Sex: 137 males, 91 females Age: 36.5±11.1
	Interventions	Amisulpride 800 mg/d or risperidone 8 mg/d, flexible dosing schedule
	Rating scale	BPRS
	Sponsor	Sanofi Synthélabo
Puech 1998(33)	Methods	Double-blind RCT Duration: 4 weeks ITT and OC analysis
	Participants	Schizophrenia, chronic or subchronic, with acute exacerbation of paranoid, disorganised or undifferentiated (DSM-III-R), four core BPRS productive symptoms≥12 with at least 2 of these items≥4 Setting: inpatients N: 258 Sex: 155 males, 103 females Age: 36±11.3
	Interventions	Amisulpride 400 mg/d, 800 mg/d, 1200 mg/d or haloperidol 16 mg/d, fixed dosing schedule (amisulpride 100 mg/d group was excluded)
	Rating scale	BPRS
	Sponsor	Sanofi Synthélabo
Schennach-Wolf 2010(34-36)	Methods	Double-blind RCT Duration: 8 weeks ITT analysis
	Participants	Schizophrenia (ICD-10), first-episode Setting: inpatients N: 224 Sex: 131 males, 93 females

		Age: 30.64±9.95
	Interventions	Risperidone 2-8 mg/d or haloperidole 2-8 mg/d, flexible dosing schedule
	Rating scale	PANSS
	Sponsor	No
Sechter 2002(37)	Methods	Double-blind RCT Duration: 6 months (response was assessed at 6th week for our analysis) ITT and OC analysis
	Participants	Schizophrenia, paranoid, disorganized, undifferentiated, or residual type (DSM-IV), chronic (disease duration of at least two years), PANSS between 60-120, recent deterioration needing a change in treatment Setting: inpatients and outpatients N: 310 Sex: 170 males, 140 females Age: 38.4±10.8
	Interventions	Amisulpride 400-1000 mg/d or risperidone 4-10 mg/d, flexible dosing schedule
	Rating scale	BPRS
	Sponsor	Sanofi Synthélabo
Tollefson 1997(38)	Methods	Double-blind RCT Duration: 6 weeks ITT and OC analysis
	Participants	Schizophrenia, schizophreniform disorder, or schizoaffective disorder (DSM-III-R), BPRS (0-6)≥18 and/or intolerant of current antipsychotic therapy Setting: inpatients and outpatients N: 1996 Sex: 1296 males, 700 females Age: 38.6±11.4
	Interventions	Olanzapine 5–20 mg/d or haloperidol 5–20 mg/d, flexible dosing schedule
	Rating scale	PANSS
	Sponsor	Eli Lilly Company
Tollefson 2001(39)	Methods	Double-blind RCT Duration: 18 weeks, possible open label extension up to 3 years (response was assessed at 6th week for our analysis) ITT and OC analysis
	Participants	Schizophrenia (DSM-IV), BPRS(1-7)≥45 & at least 2 PANSS Positive symptoms≥4, clinically resistant to previous treatments Setting: inpatients and outpatients N: 180 Sex: 115 males, 65 females Age: 38.6±10.6
	Interventions	Olanzapine 15–25 mg/d or clozapine 200–600 mg/d, flexible dosing schedule
	Rating scale	PANSS
	Sponsor	Eli Lilly Company
Tran 1997(40)	Methods	Double-blind RCT Duration: 28 weeks (response was assessed at 6th week for our

		analysis) ITT and OC analysis
	Participants	Schizophrenia, schizophreniform disorder, or schizoaffective disorder (DSM-IV), BPRS(1-7)≥42 &Setting: inpatients and outpatients N: 339 Sex: 220 males, 119 females Age: 36.2±10.7
	Interventions	Olanzapine 10-20 mg/d or risperidone 4-12 mg/d, flexible dosing schedule
	Rating scale	PANSS
	Sponsor	Eli Lilly Company
Wetzel 1998(41)	Methods	Double-blind RCT Duration: 6 weeks ITT and OC analysis
	Participants	Schizophrenia, paranoid or undifferentiated (DSM-III-R), BPRS (1-7) ≥36 Setting: inpatients N: 133 Sex: 74 males, 58 females Age: 34.3±10.1
	Interventions	Amisulpride 1000 mg/d or flupenthixol 25 mg/d, fixed dosing schedule (could be adjusted in case of side effects to a minimal dose of 600 mg/d and 15 mg/d respectively)
	Rating scale	BPRS
	Sponsor	Sanofi Synthélabo

BID=twice daily, BPRS=Brief Psychiatric Rating Scale, BPRS-C=Brief Psychiatric Rating Scale for Children, CGI-S=Clinical Global Impression-Severity, DSM-III-R, -IV=different versions of the Diagnostic and Statistical Manual of Mental Disorders, FGAs=First Generation Antipsychotics, ICD=International Classification of Diseases, ITT=Intention-To-Treat, OC=Observed Cases, PANSS=Positive and Negative Syndrome Scale, QD=every day, RCT=Randomized Controlled Trial, SGAs=Second Generation Antipsychotics

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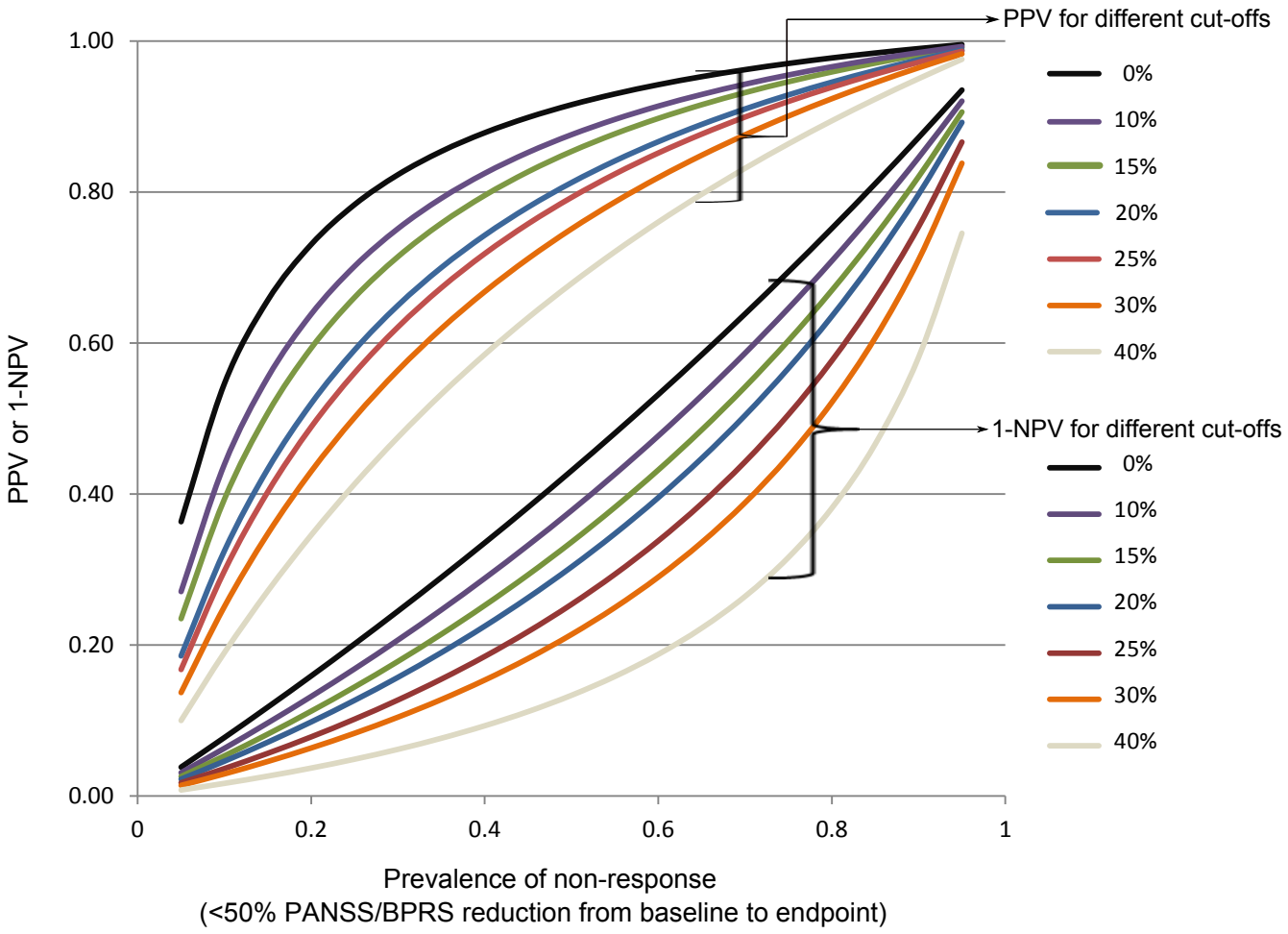
Figure S1. Predictive values in dependence of the prevalence of non-response at endpoint for the different cut-offs of the index test at week 2



As Positive predictive value (PPV) and Negative predictive value (NPV) depend on the prevalence of the condition (here non-response defined as less 50% PANSS/BPRS reduction from baseline to endpoint), we plotted the values of PPV (upper curves) and 1-NPV (lower curves) versus the prevalence of non-response. The plot shows that, as the prevalence of non-response increases, PPV increases whereas NPV (here shown as 1-NPV) decreases. Different colours correspond to different cut-offs of the index test.