Data supplement for Howes et al., Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology. Am J Psychiatry (doi: 10.1176/appi.ajp.2016.16030319)

Supplementary Information

Survey Questionnaire

Please note: The survey is intended to inform the development of a consensus statement on RESEARCH definitions. The consensus statement is intended to aid the design and reporting of research in treatment response and resistance by providing agreed criteria and definitions. As such all the questions apart from the final one pertain to RESEARCH setting

Terminology

1. Which is your preferred term to describe schizophrenia that has not responded to adequate treatment (excluding clozapine): *Treatment resistant/ Treatment refractory/ Treatment non-responsive/ Treatment poorly responsive/ Other (please specify)*
2. Should the word "antipsychotic" be specified in the terminology?
3. Should sub-specifiers be used? eg to define whether this is based on poor response of positive symptoms alone OR negative symptoms alone OR meets criteria for poor response on both positive and negative symptoms
4. If yes, please indicate which sub-specifiers should be used (please check all that apply): *Positive symptoms only/Negative symptoms only/ Cognitive symptoms only/ Positive and negative symptoms/ Positive and cognitive symptoms/ Negative and cognitive symptoms/ Positive, negative and cognitive symptoms/ Other (please specify)*

Definition of treatment resistance for research studies

5. With regard to symptom rating, should one standard rating scale (eg PANSS, CGI or BPRS) be used? Or should an equivalent threshold (eg at least moderate severity) be specified for use across rating scales?
6. If one standard rating scale is used, what should it be?
7. Threshold of current symptoms. Should this be: At least moderate severity?*At least severe severity?/ Highest rating severity?/ Other (please specify)*
8. Minimum duration of current symptoms at the given threshold severity or greater since achieving a therapeutic antipsychotic treatment dose. Should this be: *At least one week?/ At least 4 weeks?/ At least 6 weeks?/At least 8 weeks?/At least 12 weeks?/ At least 23 weeks?/ Another (please specify)/ Other*
9. Number of symptom items (eg: PANSS P1, P2, P3, P4, P5, P6, P7) scoring at threshold: *Global assessment only/ ≥1 item above threshold/ ≥2 items above threshold/ ≥3 items above threshold/ ≥ 4 items above threshold/ Other (please specify)*
10. Minimum duration at a therapeutic dose (ie not including any titration) of an adequate antipsychotic treatment episode. Should this be at least: *4 weeks/ 6 weeks/ 8 weeks/ 12 weeks/ other*
11. Should there be a requirement for functional impairment as well?
12. If yes, how should this be measured*? GAF/ Using the FACT-sc/ WHODAS 2.0 (DSM 5 page 747)/ Other (please specify)*
13. If functional impairment is required, what level of current impairment is required? *At least mild/ At least moderate/ At least severe/ The most severe category/ Other*
14. Should there be a requirement that the symptoms are causing distress?
15. If yes, how should this be measured?
16. Given there is a spectrum of adherence, what is the minimum level of adherence that should be established for a treatment episode to be deemed adequate? *100% of prescribed doses taken at the prescribed time/ 90-100%/ 80-90%/ 70-80%/ 60-70%/ 50-60%*

17. Given that most ORAL antipsychotics have a range of therapeutic doses, what dose should be deemed the minimum therapeutic dose for a treatment episode to be deemed adequate for ORAL treatment? *The lowest daily licensed dose specified as within the therapeutic range?/ The mid-point daily dose in the licensed therapeutic range?/ The maximum daily licensed dose in the therapeutic range?/ A minimum dose as expressed as chlorpromazine equivalents?/ A minimum dose as expressed as haloperidol equivalents?/ Other (please specify)*
18. Given that most INJECTABLE antipsychotics have a range of therapeutic doses, what dose should be deemed the minimum therapeutic dose for a treatment episode to be deemed adequate for DEPOT/LONG ACTING INJECTABLE TREATMENT? *The lowest dose and least frequent dose frequency within the licensed therapeutic range?/ The dose closest to the middle dose and dose frequency within the licensed therapeutic range?/ The maximum dose at the most frequent dose frequency within the licensed therapeutic range?/ A minimum dose as expressed as chlorpromazine equivalents?/ A minimum dose as expressed as haloperidol equivalents?/ Other (please specify)*
19. If expressed as chlorpromazine or haloperidol equivalents specify minimum: What method of converting a given drug dose into equivalents? (please specify a reference if possible)
20. Should trials aborted for intolerability below the dose threshold as determined by the group be counted as one of the adequate treatment trials for the purposes of determining treatment resistance?
21. How should adherence to antipsychotic treatment be determined for oral treatment*: By patient self-report alone / Dispensing chart review alone/ Pill count alone/ Serum trough antipsychotic level above a threshold on one occasion alone/ Serum trough antipsychotic level above a threshold on at least two separate occasions alone/ Dispensing chart review and pill count both at minimum adherence/ Dispensing chart review and pill count both at minimum adherence and serum antipsychotic level above a threshold on at least one occasion/ Dispensing chart review and pill count both at minimum adherence and serum trough antipsychotic level above a threshold on at least two separate occasions/ Other*
22. If serum antipsychotic level is used what threshold is used: *The lowest therapeutic level specified in a guideline (eg Maudsley Prescribing Guidelines)/ A consensus statement/ The lowest therapeutic level specified in a recent reference paper/ Other (please specify)*
23. How should adherence to antipsychotic treatment be determined for long-acting injectables? By patient self-report alone/ Dispensing chart review alone/ Patient self report + dispensing chart+ family report/ Other (please specify)
24. Should there be a requirement that at least one treatment episode uses a route with assured adherence, such as a long acting injectable?
25. Should patients have failed different “classes” of antipsychotics (eg first generation and second generation antipsychotics) to meet resistance criteria?
26. What different classes should be used?
27. What is the minimum number of adequate antipsychotic treatment episodes with different antipsychotics to establish resistance: *1/2/3/4/other*
28. Given that some patients may have shown an initial response to antipsychotic treatment followed by subsequent inadequate response to subsequent treatment, should there be a further sub-specifier for this?
29. If yes, should (check all that apply): *Primary be used to denote inadequate documented response at during first episode?Secondary to denote initial response with subsequent development of treatment resistance? Unknown to specify that this was not possible to determine? Other (please specify)*
30. Once a treatment episode has been deemed as adequate how should response be determined retrospectively (please check all that apply)? *From note review? From patient interview bench-marked against current symptoms? From patient and staff interview? Other (please specify)*
31. Should there be a requirement for the prospective assessment of inadequate response?
32. If yes, for how many treatment episodes: *One oral antipsychotic/ One long-acting injectable antipsychotic/ Two different antipsychotics (oral or injectable)/ More than two different antipsychotics/ Other (please specify)*
33. Should there be a requirement for pharmacokinetic factors to be evaluated?
34. Should lack of response to a course of psychological therapy be a requirement for non-pharmacological factors?
35. Should other treatments be a requirement for non-pharmacological factors?

Definition of treatment responders for comparative studies

36. Given that there is a continuum of response, should there be a definition of treatment RESPONDERS as well (e.g. for comparative studies)?
37. If yes: *Total symptom severity below a threshold? No individual items above a rating of mild? Meets remission criteria (e.g. Andreassen remission criteria)?Other*
38. What cut-off should be used for the minimum duration of response? At least....
6/8/12/20/26weeks/other
39. Should a minimum level of function be required?
40. If yes what minimum level of function? At least.... *Moderate/ Good/ Very good/ Exceptional*
41. Given that there is a continuum of non-response, should degree of resistance be specified?
42. If yes, how should it be specified? *Severity of current symptoms/ Degree of change from baseline symptoms/ Number of failed adequate treatment episodes/ Severity of functional impairment/ other*
43. If yes, how should the continuum be graded? *a) Two levels of severity (mild-moderate/severe treatment resistance)/ b) Three levels of severity (mild/moderate/severe treatment resistance)*
44. Should a separate, less prescriptive definition for refractory schizophrenia be specified for clinicians to use in day-to-day practice?
45. If yes, what should be dropped from the definition for research studies? *Minimum symptom severity/ Minimum treatment duration of adequate treatment/ Minimum number of different adequate antipsychotic treatment episodes/ Requirement to determine adherence/ Other*
46. Is there anything that is missing from the questions?

Survey Results

The survey results listed below provided the basis for the initial set of criteria that were refined during a series of further discussions, explaining some isolated deviations of the final criteria from the survey results (i.e., minimum symptom duration (2.3.), stricter criteria (3.5.), functional threshold in patients with adequate treatment response (4.2.)).

1. Terminology

1.1 A number of terms, such as treatment resistant or treatment refractory, have been used in the literature to describe individuals with schizophrenia who have not responded to serial trials of different treatments. There was clear consensus that the term 'treatment resistant schizophrenia' be used with 52% of respondents selecting this term. No alternative term received greater than 17% of votes.

1.2 There was less clear agreement as to whether the word 'antipsychotic' should be included in the term with 52% of respondents supporting the use of the term "Antipsychotic resistant schizophrenia".

2. Quantifying Clinical Impairment

2.1 Symptom domains: Individuals with schizophrenia may show treatment resistance primarily in specific symptom domains. 59% of respondents thought this should be reflected in the terminology, and 53% of these stated that the domains specified should be 'positive', 'negative' and 'cognitive'.

2.2 Symptom severity: A wide variety of methods exist to quantify psychiatric symptoms. 65% of respondents believed that it was preferable to specify a threshold that could be applied across multiple clinical rating scales as opposed to insisting on a particular rating scale. 65% of respondents believed that this general threshold should be set at symptoms of "at least moderate severity".

2.3 Symptom duration: Regarding the duration of current symptoms, the median response was that symptoms should have been present at the above severity for 6-8 weeks despite receiving a therapeutic antipsychotic dose.

2.4 Functional impairment: 54% of respondents stated that there should also be a requirement for functional impairment in order for an individual to be considered treatment resistant. 73% of these respondents felt this was best measured using the Global Assessment of Functioning (GAF) and 63% believed the level of impairment should be "at least moderate".

2.5 Subjective distress: Lack of insight is a common feature in individuals with schizophrenia; some patients may not be clearly distressed by their symptoms, and concerns may primarily be raised by others. 64% of survey respondents did not feel that there should be a requirement for symptoms to be causing distress.

2.6 Grading degree of resistance: Treatment resistance is mostly treated as a binary variable in clinical research although a continuum may better reflect clinical reality. 81% of respondents believed that a degree of resistance should be specified and 89% of these believed this should be based on the severity of current symptoms. 53% voted that this continuum should be divided into three (mild/moderate/severe), while 47% felt 2 categories were sufficient (mild-moderate/severe).

2.7 Late onset resistance: 50% supported the addition of a further specifier to denote initial response followed by subsequent treatment resistance.

3. Defining Adequate Treatment

3.1 Duration: Regarding duration of treatment, the median response was that any past antipsychotic treatment episode should have lasted at least 6 weeks, at a therapeutic dose, in order to be deemed 'adequate'.

3.2 Dose: In order for a treatment episode to be deemed therapeutic, the majority (62%) of respondents stated that the minimum dose of prescribed oral antipsychotic should the mid-point daily dose in the licensed therapeutic range. A similar proportion (65%) of respondents believed the same specification was also appropriate for injectable antipsychotics. 69% stated that if a trial had to be aborted secondary to intolerability it should not count as an adequate treatment trial.

3.3 Past treatment episodes: 73% of respondents stated that two treatment episodes were sufficient to demonstrate treatment-resistance, while 27% believed at least 3 episodes should be required. In order to assess the response to past treatment episodes, 62% stated that patient and staff interview was an appropriate method.

3.4 Adherence: Due to lack of illness insight, side effect burden, and cognitive impairment, non-adherence is a significant problem in the treatment of schizophrenia. Regarding what level of adherence deemed a trial adequate, the median response was that adhering to the prescribed dose at least 80-90% of the time was sufficient. There was a wide range of responses as to how best assess adherence to oral medication; 48% stated that the measurement of serum antipsychotic levels should play a role and the same proportion stated that pill count and dispensing chart reviews should be included. In the case of long-acting injectables, 52% felt a review of the dispensing chart alone was sufficient.

3.5 Stricter criteria: 38% of respondents believed that at least one treatment episode should use a route with assured adherence, such as a long-acting injectable antipsychotic. 23% stated that patients should have failed different classes (i.e., first- and second-generation) of antipsychotics to be classified as treatment resistant. 38% felt that there should be a requirement for the prospective assessment of inadequate response. 35% felt there should be a requirement for pharmacokinetic factors to be evaluated. 4% stated that a lack of response to non-pharmacological factors (including psychological therapies) should be required.

4. Defining adequate treatment response

4. 96% felt that a definition should also be specified for patients with adequate treatment response. 46% felt this should require total symptom severity to be below a certain threshold while 36% felt that it should require patients to meet set remission criteria (e.g., Andreasen criteria (124)).

4.1 Duration of response: The median suggested duration of sustained response for a patient to be considered a responder was 12 weeks.

4.2 Functional assessment: 62% felt that for a patient to be considered to have responded a minimum level of function should be required, and 54% felt that this should be at least 'moderate'.*

5. Definitions in clinical practice
35% of respondents supported the use of a separate, less prescriptive definition for clinicians to use in day-to-day practice.

*As moderate functional impairment is also a criterion for treatment resistance, meaning there would be a risk of overlap between the two groups. In view of this it the threshold for adequate treatment response was raised to mild functional impairment.

FIGURE S1. Flowchart showing the number of studies identified during the search and screening process used to identify studies for the systematic review

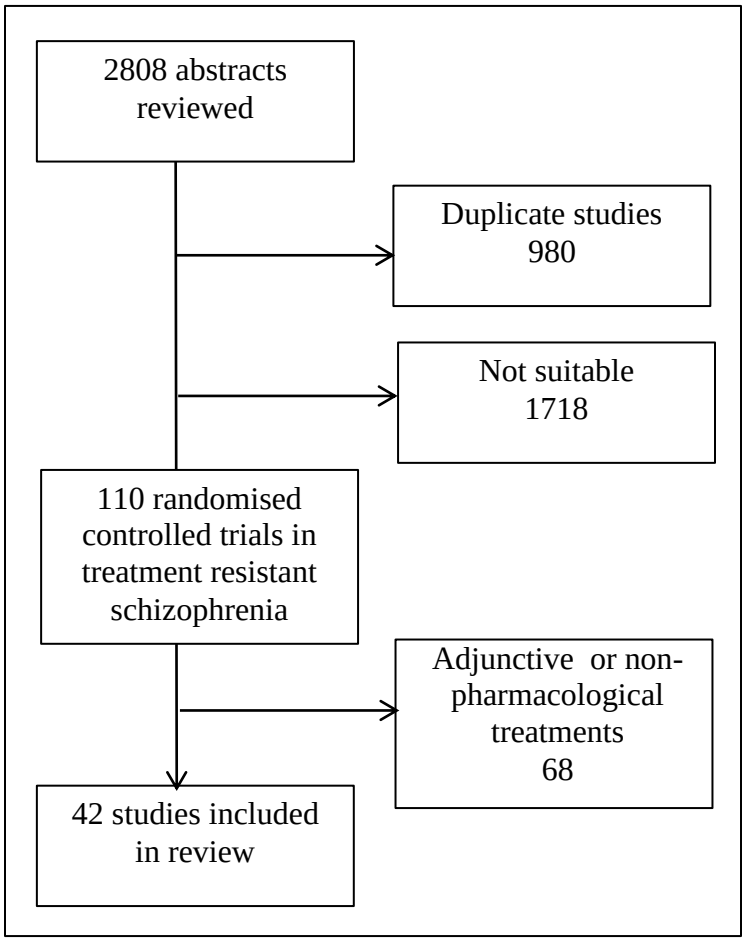

TABLE S1. Definitions of treatment resistant schizophrenia used in clinical trials

AP – Antipsychotic; BPRS- Brief Psychiatric Rating Scale; CGI – Clinical Global Impression; CGI-S- CGI-Severity; CPZ- Chlorpromazine equivalents; NS – Not Specified; PANSS – Positive and Negative Syndrome Scale; RISP – Risperidone equivalents; SANS – Scale for the Assessment of Negative Symptoms. *not further specified

	Requirements of previous treatment				Severity of illness				
Study	**Minimum number of failed APs**	**≥2 APs from different classes**	**Adequate treatment episode duration**	**Dose**	**Current symptoms**	**Other criteria**	**Prospective assessment of treatment resistance?**	**Assessment of past adherence**	**Operationalized Criteria used?**
Claghorn et al., 1987 (3)	2	No	NS	NS	Score ≥4 in ≥3 of BPRS items 3,4,10,11,12 &15.	DSM-II schizophrenia. Must have had neurological reaction (TD or EPSE) to previous treatment. Current hospitalisation <6mths	No	NS	No
Huang et al., 1987(89)	2	No	≥6 mths total	≥60mg thiothixene	"Psychotic condition sufficient to require hospitalisation" *	'Mentally ill'* for >2 years	Yes – 2 weeks thioxene 60mg/day	NS	No
Kane et al., 1988(4)	3 within 5 years	Yes	6 weeks	≥1000 mg CPZ	18 item BPRS≥45 with ≥4 in≥2psychotic items. CGI-S≥4	No relief or period of good functioning in previous 5 years	Yes – to 6 weeks haloperidol treatment up to 60mg/day	NS	Yes
Breier et al., 1994 (90)	2	No	6 weeks	NS	Score of ≥8 on BPRS positive items (or ≥4 on a single item) OR score ≥20 on SANS (or ≥2 on a global item)	-	Yes – 6-week trial 20mg/day fluphenazine	NS	No
VanderZwaag et al., 1996 (91)	2	No	NS	NS	"Failed to respond"*	-	No	NS	No
Hong et al., 1997 (92)	2 within 6 mths	Yes	NS	≥1000 mg CPZ	≥5 on ≥2 of BPRS positive items (3,4,11,12,15)	-	Yes – 6 weeks haloperidol 60mg/day	NS	Yes
Mercer et al., 1997 (93)	NS	No	NS	NS	May et al Criteria(94) – scores of 4,5 or 6 for ≥6months and <5 years.	-	No	NS	No
Meyer-Lindenberg et al., 1997 (95)	2	No	≥3 weeks	NS	"Nonresponse or intolerance"*	-	No	NS	No
Rosenheck et al., 1997 (96)	2	No	Not specified	≥1000 mg CPZ	"Severe symptoms, indicated by scores on the BPRS and the CGI"	30-364 days hospitalised during past year. Serious social dysfunction for the previous two years.	No	NS	Yes
Bondolfi et al., 1998 (97)	2	No	4 weeks	'appropriate'*	PANSS total 60-120	Intolerance counts as adequate treatment trial	No	NS	No
Conley et al., 1998 (98)	2 within 5 years	Yes	6 weeks	≥1000 mg CPZ	≥45 on BPRS total AND ≥4 on 2 of the BPRS positive items AND CGI-S≥4.	No good functioning in past 5 years	Yes – Haloperidol 10-40mg/day for 6 weeks.	NS	Yes
Breier et al., 1999 (99)	1	No	6 weeks	'therapeutic'*	Score of ≥8 on BPRS positive items OR score ≥20 on SANS (or ≥2 on a global item)	-	Yes – Fluphenazine 20mg/day for2 weeks	NS	No
Simpson et al., 1999 (100)	3	No	6 weeks	≥1000 mg CPZ	BPRS≥45 with ≥4 in≥2psychotic items. CGI-S≥4	Kane et al (101)criteria	Yes – 4 week period of normal medication observed as inpatient, then 4 weeks of haloperidol 10mg	NS	Yes
Wirshing et al., 1999 (102)	3 in last 5 years	Yes	6 Weeks	≥1000 mg CPZ	BPRS ≥45, ≥4 in ≥2 psychotic items. CGI-S≥4	Modified Kane et al (101)criteria	No	NS	Yes

Wahlbeck et al., 2000 (103)	2 within 6 mths	Yes	6 weeks	≥1000 mg CPZ	"Persistent psychotic symptoms"*	-	Yes – haloperidol up to 50mg/day for 6 weeks	NS	No
Azorin et al., 2001 (104)	2	Yes	6 weeks	≥20mg Haloperidol for ≥1 trial	18 item BPRS≥45 with ≥4 in≥2psychotic items. CGI-S≥4	Continual antipsychotic treatment for past 6 months without improvement. No period of good functioning for a) 24 months despite treatment with 2 antipsychotics OR b) 5 years despite treatment with 3 antipsychotics	No	NS	Yes
Kane et al., 2001 (105)	2	No	6 weeks	≥600 mg ≤500mg CPZ	Score of ≥4 on 1 of the positive BPRS items	-	No	"Excluded if evidence that refractoriness was related to medication non-compliance "	Yes
Smith et al., 2001(106)	2	No	Not specified	NS	"Current active positive or severe negative symptoms which impact on functioning and prevent discharge"*	Continuously hospitalised of ≥1 year.	No	NS	No
Tollefson et al., 2001 (107)	2	Yes	6 weeks	≥500 mg CPZ	Score of ≥45 BPRS total and ≥4 on one of the PANSS positive items.		No	NS	Yes
Zhang et al., 2001 (108)	3	No	3 months	≥1000 mg CPZ	CGI-S≥4	Duration of illness ≥5 years	No	NS	Yes
Altamura et al., 2002 (109)	2	Yes	6 weeks (total treatment)	"Therapeutic"*	(Total BPRS positive of ≥8 or ≥4 on individual items) AND (total SANS ≥20 or ≥2 on a global item)	-	No	NS	No
Liberman et al., 2002(110)	3 in past 5 years	Yes	6 weeks	≥1000 mg CPZ	Modified Kane et al(101) criteria	Intolerance counts as adequate treatment trial	3 weeks of Haloperidol 15-30mg/day	NS	Yes
Volavka et al., 2002 (111)	1	No	6 weeks	≥600 mg CPZ	Persistent positive symptoms. ≥60 on PANSS	Poor functioning ≥ 2 years defined as lack of competitive employment/ enrolment in an academic l program and not having age-expected interpersonal relations with someone outside the biological family of origin. Patients described as "sub-optimal responders"	No	NS	Yes
Conley et al., 2003 (112)	As in Conley et al. 1998				As in Conley et al. 1998	-	Unclear	NS	Yes
Potkin et al., 2003 (113)	NS	No	NS	NS	"Treatment resistant": not otherwise defined	-	No	NS	No
Bitter et al., 2004 (12)	1	No	4-6 weeks	400-600 mg CPZ	BPRS≥42	Discontinuation due to intolerability considered valid trial	No	NS	Yes
Jackson et al., 2004 (114)	2	No	6 weeks	≥1000 mg CPZ	"Failure to respond"*	≥1 antipsychotics must be a nonphenothiazine. Treatment intolerant patients included. Current hospitalisation ≥ 4 months. Hospitalised for ≥2 of past 5 years.	No	NS	No
Moresco et al., 2004 (115)	2	Yes	6 weeks	≥500mg CPZ	BPRS≥27	-	No	NS	Yes

Buchanan et al., 2005 (116)	2	Yes	6 weeks	"therapeutic"*	(≥8 on BPRS positive items or ≥4 on any individual item) OR (≥20 on SANS or ≥2 on a global item)	Patients described as 'partial responders'	4 weeks of 20mg/day fluphenazine	NS	Yes
Conley et al., 2005 (117)	2	No	6 weeks	≥600mg CPZ	≥45 on BPRS total AND ≥4 on 2 of the BPRS positive items AND CGI-S≥4.	No period of good functioning in the past 5 years	4-6 weeks trial of olanzapine or a typical antipsychotic	NS	Yes
McGurk et al., 2005 (118)	2	No	NS	≥600mg CPZ AND 250-500mg CPZ	≥2 on one of the BPRS positive items OR ≥2 on a SANS global item	Participants living in community or potentially dischargeable	No	NS	No
Alvarez et al., 2006 (119)	NS	No	NS	NS	SANS summary score≥ 10	Only patient on 1st generation antipsychotics included. Patients must not have been hospitalised in the past 3 months. Studying persistent negative symptoms as opposed to clear resistance	No	NS	No
Kane et al., 2006 (120)	2	No	3 x 6 week period	NS	No significant symptomatic improvement. ≥45 on BPRS AND ≥4 on PANSS core psychosis items AND ≥4 on CGI-S	-	6 week trial of 10-30mg haloperidol/day	fNS	No
Lal et al., 2006 (121)	3	Yes	6 week	≥1000 mg CPZ	BPRS≥45 and ≥4 on 2 of the positive items	No good functioning past 5 years. Kane et al (101) criteria.	7 week trial haloperidol up to 60mg/day	NS	Yes
Kane et al., 2007 (122)	2	No	6 weeks	"adequate"*	PANSS total≥75 AND ≥4 on at least 2 positive items AND CGI-S≥7	Must have had at least one typical antipsychotic. Treated as an outpatient for at least 1 continuous 3-month period during the 2 years prior to study entry	6 week trial of olanzapine (10-20mg) or risperidone (2-8mg)	NS	No
Lewis et al., 2006 (123)	2	No	NS	NS	NS	Responsible clinician electing to change current drug because of poor response, and considering clozapine	No	NS	No
Sirota et al., 2006 (124)	2	No	4-6wks	400-600mg CPZ	PANSS negative≥15 AND SANS≥60	-	No	NS	Yes
Meltzer et al., 2008 (125)	2	Yes	6wks	"adequate"*	≥4 on at least 2 of PANSS positive items	Modified Kane et al (101)criteria	No	NS	No
Sacchetti et al., 2009 (126)	3 in past 5 years	No	6wks	Manufacturer proposed range	PANSS ≥80 AND CGI-S≥4	Stopping an antipsychotic due to intolerance counts as adequate trial	No	NS	Yes
Kane et al., 2011 (127)	1 in past 6 months	No	"adequate"*	"adequate"*	PANSS≥60 and ≥8 on any 2 BPRS positive items	-	4-6 wk haloperidol 10-30mg/day	NS	No
Lindenmayer et al., 2011 (128)	1	No	6 weeks	≥600mg CPZ	Presence of persistent positive symptoms and PANSS≥60	Poor functioning for the past two years (lack of employment, education and interpersonal relations)	4 weeks quetiapine 600mg/day	NS	Yes
Meltzer et al., 2014 (129)	2	No	"adequate"*	"adequate"*	≥4 on at least one PANSS delusion/suspiciousness/hallucinations	-	No	"Patients with a history of non-adherence were excluded"	No