Supplementary Online Content

Antipsychotic drugs versus barbiturates or benzodiazepines used as active placebos for schizophrenia: a systematic review and meta-analysis

eAppendix 1. PRISMA checklist

1. PRISMA checklist

Prisma checklist according to Moher et al. 2009.(Moher *et al.*, 2009)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5, eAppendix 2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5, eAppendix 3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	eAppendix 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7, eAppendix 4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8

eAppendix 1. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9, PRISMA flow chart in Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1, eAppendix 4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10, risk of bias graph in Figure 2, eAppendix 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 3-4, eAppendix 5
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency	11-13, Figure 3-4, eAppendix 5-6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12-13, risk of bias graph in Figure 2, eAppendix 6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11-13. eAppendix 5
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-16, eAppendix 6
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16-18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	19

2. References

Moher, D., Liberati, A., Tetzlaff, J. & Altman, D. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* **6**, e1000097.

eAppendix 2. Protocol of the systematic review

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1. Registered protocol of the systematic review

The a priori written protocol of the review was registered on PROSPERO database, with a registration number CRD42018086263.

Title

Antipsychotic drugs versus barbiturates or benzodiazepines as active placebos for schizophrenia

Spyridon Siafis, John Davis, Georgios Papazisis, Stefan Leucht

Citation

Spyridon Siafis, John Davis, Georgios Papazisis, Stefan Leucht. Antipsychotic drugs versus barbiturates or benzodiazepines as active placebos for schizophrenia. PROSPERO 2018 CRD42018086263 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018086263

Review question

To compare the efficacy of antipsychotics with barbiturates or benzodiazepines for schizophrenia.

Searches

1. We will search ClinicalTrials.gov, the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, MEDLINE, PsycINFO, PubMed and WHO ICTRP, up to 9 January 2018. Regarding barbiturates, there will be no restrictions in terms of date/time, language, document type, or publication status. Regarding benzodiazepines, the search will be built on the existing Cochrane review (Dold *et al.*, 2012), and an updated search of the literature published after 2010 will be conducted, with no language, document type or publication status limitations. We will follow the Cochrane Handbook (Higgins and Green, 2011), and the PRISMA (Moher *et al.*, 2009) guidelines.

2. The reference lists of the studies selected for inclusion will also be inspected.

3. A hand search of the book chapter on the treatment of schizophrenia in the "Diagnosis and Drug Treatment of Psychiatric Disorders" (Klein and Davis, 1969), will also be undertaken, as it includes relevant trials rarely ever found in the electronic databases.

Types of study to be included

Randomized controlled trials (RCTs). Both blinded and open RCTs will be included, but open RCTs will be excluded in the sensitivity analysis. The minimum duration of follow-up will be 3 weeks, as shorter trials are unlikely to find significant differences in terms of the core symptoms of schizophrenia (McMahon *et al.*, 2008). In a similar vein, we are not interested in short-term sedation of acutely ill (agitated) patients for which benzodiazepines and barbiturates are likely to be effective. Some of these studies will have an initial phase of a few days, and will then have a longer-term naturalistic follow-up (for example, the TREC studies by the Cochrane Collaboration (Alexander *et al.*, 2004; Huf *et al.*, 2002), which will also be excluded for the same reasons. For cross-over studies, the first cross-over phase will be used in order to avoid any carry-over effects. In the case of multiple treatment groups of either antipsychotics or benzodiazepines/barbiturates, the various treatment arms will be presented and combined when possible, as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2011).

Condition or domain being studied

Schizophrenia.

Participants/population

Patients with acute forms (study-defined) of schizophrenia or related disorders (including schizophreniform, schizoaffective and delusional disorder, because there is no evidence that the latter schizophrenia-like psychoses are caused by fundamentally different disease processes or require different treatment approaches), irrespective of age, gender, ethnicity, chronicity of illness, previous treatments, setting and means of diagnosis. We will exclude studies in stable patients (study-defined), because such studies are usually undertaken to examine relapse prevention, which is not the focus of this review. We will also exclude studies in which all patients were required to have a concomitant physical illness as an inclusion criterion. Studies in which less than than 20% of the participants were suffering from psychiatric disorders other than schizophrenia (e.g. depression or mental

retardation) will be acceptable. We will include trials irrespective of the diagnostic criteria used. It is a general strategy of the Cochrane Schizophrenia Group (CSG) to include studies other than those, which have used specific diagnostic criteria such as ICD-10 or DSM-V, because these criteria are not meticulously used in clinical routine. This decision should increase the generalizability of the findings.

Intervention(s), exposure(s)

Any antipsychotic drug at any dose range and administered via any form of application, except for short-term intramuscular injections, which are used for sedation purposes.

Comparator(s)/control

Any barbiturate or benzodiazepine at any dose range and administered via any form of application, except for short-term intramuscular injections, which are used for sedation purposes.

Primary outcome(s)

Response to treatment as defined in the original studies. Any definition of response in the individual studies will be accepted, and the number of patients who improved/did not improve in the antipsychotic and barbiturate or benzodiazepine arms will be determined.

Timing and effect measures

We will pool all studies, and will take the endpoint results. In addition, all outcomes will be classified into short-term results (3 weeks-3 months) in which the primary time point will be six weeks, if available, and longer-term results (>3 months), and will be shown as subgroups in graphs.

Secondary outcome(s)

1. Overall symptoms of schizophrenia derived from rating scales, such as PANSS and BPRS. We will apply the following hierarchy: mean change of the PANSS total score from baseline to endpoint, and if not available, mean change of the BPRS, or, if again not available, the mean values at the endpoints of the PANSS/BPRS. If neither of these scales has been used, the other scales for the measurement of overall symptoms of schizophrenia will be accepted.

2. Positive and negative symptoms, as measured using relevant rating scales (e.g. the subscores of the PANSS).

3. Premature discontinuation (‘dropouts’) due to any cause, inefficacy and adverse events.

Timing and effect measures

We will pool all studies, and will take the endpoint results. In addition, all outcomes will be classified into short-term results (3 weeks-3 months) in which the primary time point will be six weeks, if available, and longer-term results (>3 months), and will be shown as subgroups in graphs.

Data extraction (selection and coding)

1. Selection of trials:

Two reviewers will independently inspect all abstracts identified in the searches. Disagreements will be resolved by discussion, and if doubt still remains, we will acquire the full article for further inspection. Once the full texts of all potentially relevant articles have been obtained, at least two reviewers will then independently decide whether they meet the predefined review criteria. Any disagreements arising at this stage of the assessment process which cannot be resolved by discussion will be resolved by consultation with a third reviewer, or by requesting further information from the study authors.

2. Data extraction:

Two reviewers will then independently extract the relevant data from all the trials selected for inclusion in the review using electronic forms. Any disagreements arising will be resolved by discussion with a third reviewer, and if this is not possible, the study authors will be contacted, and further information/clarification requested.

Risk of bias (quality) assessment

Assessment of the quality of the included studies will be conducted independently by two reviewers, with any doubts arising being resolved by discussion with a third reviewer. Random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other potential sources of bias will be assessed using the Cochrane Collaboration's risk of bias tool (Higgins and Green, 2011), and the strength of the evidence will be assessed using the GRADE approach, and the online tool GRADEpro (Schünemann *et al.*, 2013).

Strategy for data synthesis

1. Study characteristics, quality assessment and the effects of interventions in individual studies will be presented descriptively. We expect to identify old studies, which are known to suffer from poor reporting and diverse outcome measures. A meta-analysis of the useable data will be conducted, but, as we can expect that most studies will be old and insufficiently reported to allow for the calculation of effect sizes, a detailed narrative descriptive of the results of the individual studies has also been planned a priori.

2. The effect size for dichotomous outcomes will be the relative risk ratio (RR) and its 95% confidence intervals, accompanied by number-needed-to-treat to benefit/harm results (NNTB/NNTH). We prefer relative risks over odds ratios, because, despite the mathematical advantages of the latter, relative risks are more intuitive for clinicians. Everyone allocated to the intervention in a given trial will be counted whether they completed the follow-up or not, and if the authors applied such a strategy, we will use their results. If the original authors presented only the results of the per protocol or of the completer population, we will assume that those participants lost to follow-up would not have changed for a given outcome. In terms of efficacy, this means that they would be conservatively considered to have not responded to treatment. In terms of tolerability, it would mean that the participants would not have developed side-effects which we feel are appropriate, because otherwise the side-effects, many of which are rare, would be overestimated. For continuous data, standardized mean difference (SMD) will be calculated, because we expect that the studies will have used different rating scales for overall schizophrenia symptoms. Intention-to-treat data will be used whenever available, and studies which have presented per protocol data will be excluded from the sensitivity analysis. As some heterogeneity can be assumed a priori, studies will be combined using the random effects model according to DerSimonian and Laird approach, but in a sensitivity analysis of the primary outcomes, we will use a fixed effect model.

3. Missing standard deviations (SD) will be derived from the following options and in the following order: 1) from standard errors (SE); 2) from confidence intervals, t-values, or p-values; 3) by contacting the original authors for further information; 4) from SDs of other included studies using a validated imputation technique, as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2011).

4. Assessment of heterogeneity will be carried by: a) a visual inspection of forest plots; and b) by applying statistical tests (χ^2 and I^2). Potential sources of heterogeneity will be explored by re-reading the relevant trials for data extraction/entry mistakes, clinical and methodological differences, and by subgroup and meta-regression analyses.

5. Small-study effects and the possible associated publication bias will be assessed by visual inspection of funnel plots (Egger *et al.*, 1997).

Analysis of subgroups or subsets

1. Predefined subgroup analysis of the primary outcome will assess the use of benzodiazepines or barbiturates as comparators. Moreover, if the data is available, we will look at specific patient populations, such as treatment-resistant patients, patients with predominantly negative symptoms, children/adolescents and other patient subgroups, in particular to determine whether they explain the statistical heterogeneity of the results.

In addition, a priori defined meta-regression analyses will address baseline severity and antipsychotic dose in chlorpromazine equivalents according to the international consensus by Gardner et al (Gardner *et al.*, 2010).

2. A priori planned sensitivity analyses of the primary outcome will exclude open RCTs and will use a fixed effect model instead of a random effects model for the statistical analysis.

Anticipated or actual start date

21 December 2017

Anticipated completion date

eAppendix 2. Protocol of the systematic review

30 June 2018

Subject index terms

Antipsychotic Agents; Barbiturates; Benzodiazepines; Drug Therapy; Humans; Placebo Effect; Placebos; Schizophrenia; Schizophrenia Spectrum and Other Psychotic Disorders; Treatment Outcome

Date of registration in PROSPERO

24 January 2018

Date of publication of this version

12 February 2018

2. Differences between protocol and review

The following protocol changes were made post hoc. No change had an important impact on the results:

1. The search was supplemented by screening an additional previous review on benzodiazepines for schizophrenia, which contained old trials, rarely found in electronic databases (Wolkowitz and Pickar, 1991).

2. Promazine and mepazine were excluded, when we identified clear evidence that they are less efficacious than other antipsychotics (Davis *et al.*, 1989), but they were included in a sensitivity analysis of the primary outcome.

3. In the protocol, the primary outcome was response to treatment, as defined by each study. However, as in our previous meta-analysis of antipsychotic drugs versus inert placebo, two response criteria were investigated, 'good' (primary outcome) and 'any' response (Leucht *et al.*, 2017). To streamline these related reviews we used the same approach. 'Good' response was defined as either at least much improvement in the Clinical Global Impression scale (CGI) (Guy *et al.*, 1976) or at least 50% reduction of the total scores from baseline of published rating scales such as the Positive and Negative Syndrome Scale (PANSS) (Kay *et al.*, 1987), the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), Lorr's Multidimensional Scale of Rating Psychiatric Patients (MSRPP) (Lorr *et al.*, 1953) or the Psychotic Reaction Profile (PRP) (Lorr *et al.*, 1960). Validation studies suggested that these cut-offs represent clinically important response (Leucht *et al.*, 2007; Leucht *et al.*, 2012; Leucht *et al.*, 2005; Levine *et al.*, 2008). Therefore, 'good' response was selected as our primary cut-off. 'Any' response was defined as at least minimal improvement in the CGI or least 20% of the total scores of the above-mentioned scales from baseline. If these cut-offs were not available other definitions of response were also accepted, which is appropriate as long as the effect size is presented as relative risks or odds ratios (Furukawa *et al.*, 2011). When responder rates were not reported, they were imputed with a validated method (Samara *et al.*, 2013) from mean values of schizophrenia rating scales applying a validated method (Samara *et al.*, 2013).

4. Unpublished scales were excluded because they might overestimate differences in schizophrenia trials (Marshall *et al.*, 2000). This is a procedure that is generally used in reviews of the Cochrane Schizophrenia Group and us. We had forgotten to write it in the protocol.

5. Post-hoc sensitivity analyses were also conducted by excluding studies with imputed responder rates.

6. Post-hoc we analyzed for the primary outcome 'good' response, the comparisons of barbiturates versus inert placebo, phenothiazines (apart from mepazine, promazine) versus mepazine.

7. Following a reviewer's suggestion, we analysed the comparison of antipsychotics versus pooled barbiturates or benzodiazepines, in order to obtain a common estimate of the comparison antipsychotic versus GABAergic drugs. Since data for the primary cut-off of response were not available, we analyzed the secondary cut-off 'any' response.

8. Following a reviewer' suggestion, we conducted post-hoc sensitivity analyses by assuming different scenarios of standard deviation for overall symptoms.

9. Following a reviewer's suggestion, we supplementary evaluated heterogeneity using the empirical distribution of τ^2. We used this method to evaluate the heterogeneity of overall symptoms (standardized mean difference) using the available empirical distributions of tau-squared of SMDs of mental health outcomes as reported in Rhodes et al 2015 (Rhodes *et al.*, 2015).

3. References

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Leucht, S., Kane, J. M., Kissling, W., Hamann, J., Etschel, E. & Engel, R. (2005). Clinical implications of Brief Psychiatric Rating Scale scores. *British Journal of Psychiatry* **187**, 366-71.

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McMahon, R., Kelly, D., Boggs, D., Li, L., Hu, Q., Davis, J. & Carpenter, W. (2008). Feasibility of Reducing the Duration of Placebo-Controlled Trials in Schizophrenia Research. *Schizophrenia Bulletin* **34**, 292-301.

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eAppendix 3. Search strategies

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1. General search strategies

We searched ClinicalTrials.Gov, Cochrane Central Register of Controlled Trials, EMBASE, MEDLINE, PsycINFO, PubMed and WHO ICTRP on 9 January 2018 with no language, document type, and publication status limitations. Two separate searches were conducted for benzodiazepines and barbiturates (eTable 1 and eTable 2). Regarding searching for benzodiazepine, we limited the search to the literature published after 2010 to update the existing Cochrane review (older records were identified by screening the Cochrane review) (Dold *et al.*, 2012), while regarding searching for barbiturates there was no restriction in terms of data/time. We followed Cochrane Handbook (Lefebvre *et al.*, 2011) for conducting and PRISMA guideline (Moher *et al.*, 2009) for reporting the search. Search strategies developed by assistance of a medical information specialist (FS). Search results were de-duplicated in EndNote X7 and sent to two researchers for screening (SS and GA).

In addition, the book chapter on the treatment of schizophrenia in the "Diagnosis and Drug Treatment of Psychiatric Disorders" (Klein and Davis, 1969) as well as a previous review on benzodiazepines for schizophrenia, Wolkowitz OM et al 1991 (Wolkowitz and Pickar, 1991), were searched, as they include old trials rarely ever found in the electronic databases. In addition, reference lists of the studies selected for inclusion were inspected. Once the full texts of all potentially relevant articles were obtained, two reviewers (SS and GP) independently decided whether they met the predefined eligibility criteria. Any disagreements in these two stages were resolved by consultation with a third reviewer (SL).

eTable1. Electronic search resources details and number of results for barbiturates

Resource	**Time Coverage**	**Search Interface**	**#**
ClinicalTrials.Gov	Until Search Date	ClinicalTrials.Gov	15
Cochrane Central Register of Controlled Trials	Until Search Date	Cochrane Library	44
EMBASE	1974 – 2018 Week 2	Ovid SP	103
MEDLINE	1946 – Search Date	Ovid SP	284
PsycINFO	1806 – 2017 Jan Week 1	Ovid SP	82
PubMed	1946 – Search Date	PubMed	1
WHO ICTRP	Until Search Date	WHO ICTRP	11
Subtotal			540
Duplicates			97
Total (for Screening)			**443**

eTable2. Electronic search resources details and number of results for benzodiazepines (limited for studies after 2010)

Resource	**Time Coverage**	**Search Interface**	**#**
ClinicalTrials.Gov	Until Search Date	ClinicalTrials.Gov	138
Cochrane Central Register of Controlled Trials	Until Search Date	Cochrane Library	310
EMBASE	1974 – 2018 Week 2	Ovid SP	237
MEDLINE	1946 – Search Date	Ovid SP	1353
PsycINFO	1806 – 2017 Jan Week 1	Ovid SP	139
PubMed	1946 – Search Date	PubMed	29
WHO ICTRP	Until Search Date	WHO ICTRP	10
Subtotal			2216
Duplicates			775
Total (for Screening)			**1441**

2. Electronic search strategy for barbiturates

A. ClinicalTrials.Gov

Condition or Disease: Schizophrenia OR Schizoaffective OR "Schizo Affective" OR Schizophreniform OR Schizotypal OR Schizotypy OR Psychosis OR Psychotic OR Paranoid OR Delusional
Study Type: Interventional Studies (Clinical Trials)
Intervention/Treatment: Barbiturate OR Barbiturates OR Amobarbital OR Barbital OR Hexobarbital OR Mephobarbital OR Methohexital OR Murexide OR Pentobarbital OR Phenobarbital OR Primidone OR Secobarbital OR Thiamylal OR Thiobarbiturates OR Thiopental

B. Cochrane Central Register of Controlled Trials

([mh Schizophrenia] or [mh "Schizophrenia, Childhood"] or [mh "Schizotypal Personality Disorder"] or [mh ^"Psychotic Disorders"] or [mh "Paranoid Disorders"] or (Delusional Disorder* or Psychotic* or Psychosis or Psychoses or Schizoaffective or "Schizo Affective" or Schizophreniform or Schizotyp* or Schizophreni* or "Dementia Praecox" or Paranoi* or "Folie a Deux" or "Folie a Trois"):ti,ab) and ([mh Barbiturates] OR (Allobarbital OR "Ammonium Purpurate" OR Amobarbital OR Amsal OR Amylobarbitone OR Amylobeta OR Amytal OR Aprobarbital OR Barbamyl OR Barbexaclone OR Barbit* OR Barotal OR Benzobarbital OR Bomathal OR Brallobarbital OR Brevimytal OR Brevital OR Brietal OR Bucolome OR Butalbital OR Butethal OR Cyclobarbital OR Cyclopentobarbital OR Desoxyphenobarbital OR Diabutal OR Dialuric OR Diemal OR Diethylmalonylurea OR Difebarbamate OR Dormileno OR Etaminal OR Eterobarb OR Ethaminal OR Ethylbarbit* OR Eunoctal OR Evipan OR "Fali Lepsin" OR Febarbamate OR Gardenal OR Heptabarb OR Hexenal OR Hexobarbit* OR Hydroxyphenobarbital OR Hysteps OR "Isoamitil Sedante" OR Isonal OR Liskantin OR Luminal OR Meballymal OR Mebaral OR Mebubarbital OR Mebumal OR Medinal OR Mephebarbital OR Mephobarbital OR Merbarone OR Metharbital OR Methohexit* OR Methylphenobarbit* OR Misodine OR Mizodin OR Murexide OR Mylepsinum OR Mysoline OR Nembutal OR Nesdonal OR Neur-Amyl OR Novamobarb OR Penthiobarbital OR Pentobarbit* OR Pentothal OR Pentymal OR Phenemal OR Phenobarbit* OR Phenylbarbital OR Phenylethylbarbituric OR Placidel OR Primaclone OR Primidon* OR Probarbital OR Prominal OR Propallylonal OR Proxibarbal OR Quinalbarbitone OR Resimatil OR Sagatal OR Sebar OR Secbutabarbital OR Secobarbital OR Seconal OR Sertan OR Sodipental OR Surital OR Talbutal OR Thiamylal OR Thiobarbit* OR Thiobutabarbital OR Thiomebumal OR Thionembutal OR Thiopent* OR Thioquinalbarbitone OR Tiobarbital OR Transital OR Trapanal OR Veronal OR Vinbarbital OR Vinylbital):ti,ab) in Trials

C. EMBASE

1. Exp Schizophrenia/ OR Exp Schizophrenia Spectrum Disorder/ OR Schizophreniform Disorder/ OR Schizotypal Personality Disorder/ OR Psychosis/ OR Exp Paranoid Psychosis/ OR Brief Psychotic Disorder/ OR Delusional Disorder/ OR Schizoaffective Psychosis/ OR (Delusional Disorder* OR Psychotic* OR Psychosis OR Psychoses OR Schizoaffective OR "Schizo Affective" OR Schizophreniform OR Schizotyp* or Schizophreni* OR "Dementia Praecox" OR Paranoi* OR "Folie a Deux" OR "Folie a Trois").ti,ab.
2. Exp Barbituric Acid Derivative/ OR (Allobarbital OR "Ammonium Purpurate" OR Amobarbital OR Amsal OR Amylobarbitone OR Amylobeta OR Amytal OR Aprobarbital OR Barbamyl OR Barbexaclone OR Barbit* OR Barotal OR Benzobarbital OR Bomathal OR Brallobarbital OR Brevimytal OR Brevital OR Brietal OR Bucolome OR Butalbital OR Butethal OR Cyclobarbital OR Cyclopentobarbital OR Desoxyphenobarbital OR Diabutal OR Dialuric OR Diemal OR Diethylmalonylurea OR Difebarbamate OR Dormileno OR Etaminal OR Eterobarb OR Ethaminal OR Ethylbarbit* OR Eunoctal OR Evipan OR "Fali Lepsin" OR Febarbamate OR Gardenal OR Heptabarb OR Hexenal OR Hexobarbit* OR Hydroxyphenobarbital OR Hysteps OR "Isoamitil Sedante" OR Isonal OR Liskantin OR Luminal OR Meballymal OR Mebaral OR Mebubarbital OR Mebumal OR Medinal OR Mephebarbital OR Mephobarbital OR Merbarone OR Metharbital OR Methohexit* OR Methylphenobarbit* OR Misodine OR Mizodin OR Murexide OR Mylepsinum OR Mysoline OR Nembutal OR Nesdonal OR Neur-Amyl OR Novamobarb OR Penthiobarbital OR Pentobarbit* OR Pentothal OR Pentymal OR Phenemal OR Phenobarbit* OR Phenylbarbital OR Phenylethylbarbituric OR Placidel OR Primaclone OR Primidon* OR Probarbital OR Prominal OR Propallylonal OR Proxibarbal OR Quinalbarbitone OR Resimatil OR Sagatal OR Sebar OR Secbutabarbital OR Secobarbital OR Seconal OR Sertan OR Sodipental OR Surital OR Talbutal OR Thiamylal OR Thiobarbit* OR Thiobutabarbital OR Thiomebumal OR Thionembutal OR Thiopent* OR Thioquinalbarbitone OR Tiobarbital OR Transital OR Trapanal OR Veronal OR Vinbarbital OR Vinylbital).ti,ab.
3. Randomization/ OR Crossover-Procedure/ OR Double-Blind Procedure/ OR Randomized Controlled Trial/ OR Single-Blind Procedure/ OR (Random* OR Factorial* OR Crossover* OR Cross Over* OR Placebo* OR ((Singl* OR Doubl* OR Trebl* or Tripl*) adj (Mask* OR Blind*)) OR Assign* OR Allocat* OR Volunteer* OR Groups OR Trial*).mp.
4. 1 AND 2 AND 3
5. Exp Animals/ OR Exp Invertebrate/ OR Animal Experiment/ OR Animal Model/ OR Animal Tissue/ OR Animal Cell/ OR Nonhuman/
6. Human/ OR Normal Human/ OR Human Cell/

7. 5 AND 6
8. 5 NOT 7
9. 4 NOT 8
10. Limit 9 to MEDLINE
11. 9 NOT 10
12. Limit 11 to EMBASE
13. Limit 12 to Exclude MEDLINE Journals

D. MEDLINE

1. Exp Schizophrenia/ OR Schizophrenia, Childhood/ OR Schizotypal Personality Disorder/ OR Psychotic Disorders/ OR Paranoid Disorders/ OR (Delusional Disorder* OR Psychotic* OR Psychosis OR Psychoses OR Schizoaffective OR "Schizo Affective" OR Schizophreniform OR Schizotyp* or Schizophreni* OR "Dementia Praecox" OR Paranoi* OR "Folie a Deux" OR "Folie a Trois").ti,ab.
2. Exp Barbiturates/ OR (Allobarbital OR "Ammonium Purpurate" OR Amobarbital OR Amsal OR Amylobarbitone OR Amylobeta OR Amytal OR Aprobarbital OR Barbamyl OR Barbexaclone OR Barbit* OR Barotal OR Benzobarbital OR Bomathal OR Brallobarbital OR Brevimytal OR Brevital OR Brietal OR Bucolome OR Butalbital OR Butethal OR Cyclobarbital OR Cyclopentobarbital OR Desoxyphenobarbital OR Diabutal OR Dialuric OR Diemal OR Diethylmalonylurea OR Difebarbamate OR Dormileno OR Etaminal OR Eterobarb OR Ethaminal OR Ethylbarbit* OR Eunoctal OR Evipan OR "Fali Lepsin" OR Febarbamate OR Gardenal OR Heptabarb OR Hexenal OR Hexobarbit* OR Hydroxyphenobarbital OR Hysteps OR "Isoamitil Sedante" OR Isonal OR Liskantin OR Luminal OR Meballymal OR Mebaral OR Mebubarbital OR Mebumal OR Medinal OR Mephebarbital OR Mephobarbital OR Merbarone OR Metharbital OR Methohexit* OR Methylphenobarbit* OR Misodine OR Mizodin OR Murexide OR Mylepsinum OR Mysoline OR Nembutal OR Nesdonal OR Neur-Amyl OR Novamobarb OR Penthiobarbital OR Pentobarbit* OR Pentothal OR Pentymal OR Phenemal OR Phenobarbit* OR Phenylbarbital OR Phenylethylbarbituric OR Placidel OR Primaclone OR Primidon* OR Probarbital OR Prominal OR Propallylonal OR Proxibarbal OR Quinalbarbitone OR Resimatil OR Sagatal OR Sebar OR Secbutabarbital OR Secobarbital OR Seconal OR Sertan OR Sodipental OR Surital OR Talbutal OR Thiamylal OR Thiobarbit* OR Thiobutabarbital OR Thiomebumal OR Thionembutal OR Thiopent* OR Thioquinalbarbitone OR Tiobarbital OR Transital OR Trapanal OR Veronal OR Vinbarbital OR Vinylbital).ti,ab.
3. Clinical Trials as Topic/ OR Controlled Clinical Trials as Topic/ OR Cross-Over Studies/ OR Double-Blind Method/ OR Exp Randomized Controlled Trials as Topic/ OR Pragmatic Clinical Trials as Topic/ OR Single-Blind Method/ OR (Clinical Trial OR Randomized Controlled Trial OR Controlled Clinical Trial OR Pragmatic Clinical Trial).pt. OR (Random* OR Factorial* OR Crossover* OR Cross Over* OR Placebo* OR ((Singl* OR Doubl* OR Trebl* or Tripl*) adj (Mask* OR Blind*)) OR Assign* OR Allocat* OR Volunteer* OR Groups OR Trial*).mp. OR Drug Therapy.fs. NOT (Animals NOT (Humans and Animals)).sh.
4. 1 AND 2 AND 3

E. PsycINFO

Exp Schizophrenia/ OR Schizotypal Personality Disorder/ OR Schizotypy/ OR Schizoaffective Disorder/ OR Schizophreniform Disorder/ OR Paranoid Schizophrenia/ OR Psychosis/ OR "Paranoia (Psychosis)"/ OR (Delusional Disorder* OR Psychotic* OR Psychosis OR Psychoses OR Schizoaffective OR "Schizo Affective" OR Schizophreniform OR Schizotyp* or Schizophreni* OR "Dementia Praecox" OR Paranoi* OR "Folie a Deux" OR "Folie a Trois").ti,ab.

Exp Barbiturates/ OR (Allobarbital OR "Ammonium Purpurate" OR Amobarbital OR Amsal OR Amylobarbitone OR Amylobeta OR Amytal OR Aprobarbital OR Barbamyl OR Barbexaclone OR Barbit* OR Barotal OR Benzobarbital OR Bomathal OR Brallobarbital OR Brevimytal OR Brevital OR Brietal OR Bucolome OR Butalbital OR Butethal OR Cyclobarbital OR Cyclopentobarbital OR Desoxyphenobarbital OR Diabutal OR Dialuric OR Diemal OR Diethylmalonylurea OR Difebarbamate OR Dormileno OR Etaminal OR Eterobarb OR Ethaminal OR Ethylbarbit* OR Eunoctal OR Evipan OR "Fali Lepsin" OR Febarbamate OR Gardenal OR Heptabarb OR Hexenal OR Hexobarbit* OR Hydroxyphenobarbital OR Hysteps OR "Isoamitil Sedante" OR Isonal OR Liskantin OR Luminal OR Meballymal OR Mebaral OR Mebubarbital OR Mebumal OR Medinal OR Mephebarbital OR Mephobarbital OR Merbarone OR Metharbital OR Methohexit* OR Methylphenobarbit* OR Misodine OR Mizodin OR Murexide OR Mylepsinum OR Mysoline OR Nembutal OR Nesdonal OR Neur-Amyl OR Novamobarb OR Penthiobarbital OR Pentobarbit* OR Pentothal OR Pentymal OR Phenemal OR Phenobarbit* OR Phenylbarbital OR Phenylethylbarbituric OR Placidel OR Primaclone OR Primidon* OR Probarbital OR Prominal OR Propallylonal OR Proxibarbal OR Quinalbarbitone OR Resimatil OR Sagatal OR Sebar OR Secbutabarbital OR Secobarbital OR Seconal OR Sertan OR Sodipental OR Surital OR Talbutal OR Thiamylal OR Thiobarbit* OR Thiobutabarbital OR Thiomebumal OR Thionembutal OR Thiopent* OR Thioquinalbarbitone OR Tiobarbital OR Transital OR Trapanal OR Veronal OR Vinbarbital OR Vinylbital).ti,ab.

Exp Treatment Effectiveness Evaluation/ OR Mental Health Program Evaluation/ OR Placebo/ OR (Random* OR Factorial* OR Crossover* OR Cross Over* OR Placebo* OR ((Singl* OR Doubl* OR Trebl* or Tripl*) adj (Mask* OR Blind*)) OR Assign* OR Allocat* OR Volunteer* OR Groups OR Trial*).mp.
1 AND 2 AND 3

F. PubMed

("Schizophrenia"[Mesh] OR "Schizophrenia, Childhood"[Mesh] OR "Schizotypal Personality Disorder"[Mesh] OR "Psychotic Disorders"[Mesh:NoExp] OR "Paranoid Disorders"[Mesh] OR Delusional Disorder*[tiab] OR Psychotic*[tiab] OR Psychosis[tiab] OR Psychoses[tiab] OR Schizoaffective[tiab] OR "Schizo Affective"[tiab] OR Schizophreniform[tiab] OR Schizotyp*[tiab] or Schizophreni*[tiab] OR "Dementia Praecox"[tiab] OR Paranoi*[tiab] OR "Folie a Deux"[tiab] OR "Folie a Trois"[tiab]) AND ("Barbiturates"[Mesh] OR Allobarbital[tiab] OR "Ammonium Purpurate"[tiab] OR Amobarbital[tiab] OR Amsal[tiab] OR Amylobarbitone[tiab] OR Amylobeta[tiab] OR Amytal[tiab] OR Aprobarbital[tiab] OR Barbamyl[tiab] OR Barbexaclone[tiab] OR Barbit*[tiab] OR Barotal[tiab] OR Benzobarbital[tiab] OR Bomathal[tiab] OR Brallobarbital[tiab] OR Brevimytal[tiab] OR Brevital[tiab] OR Brietal[tiab] OR Bucolome[tiab] OR Butalbital[tiab] OR Butethal[tiab] OR Cyclobarbital[tiab] OR Cyclopentobarbital[tiab] OR Desoxyphenobarbital[tiab] OR Diabutal[tiab] OR Dialuric[tiab] OR Diemal[tiab] OR Diethylmalonylurea[tiab] OR Difebarbamate[tiab] OR Dormileno[tiab] OR Etaminal[tiab] OR Eterobarb[tiab] OR Ethaminal[tiab] OR Ethylbarbit*[tiab] OR Eunoctal[tiab] OR Evipan[tiab] OR "Fali Lepsin"[tiab] OR Febarbamate[tiab] OR Gardenal[tiab] OR Heptabarb[tiab] OR Hexenal[tiab] OR Hexobarbit*[tiab] OR Hydroxyphenobarbital[tiab] OR Hysteps[tiab] OR "Isoamitil Sedante"[tiab] OR Isonal[tiab] OR Liskantin[tiab] OR Luminal[tiab] OR Meballymal[tiab] OR Mebaral[tiab] OR Mebubarbital[tiab] OR Mebumal[tiab] OR Medinal[tiab] OR Mephebarbital[tiab] OR Mephobarbital[tiab] OR Merbarone[tiab] OR Metharbital[tiab] OR Methohexit*[tiab] OR Methylphenobarbit*[tiab] OR Misodine[tiab] OR Mizodin[tiab] OR Murexide[tiab] OR Mylepsinum[tiab] OR Mysoline[tiab] OR Nembutal[tiab] OR Nesdonal[tiab] OR Neur-Amyl[tiab] OR Novamobarb[tiab] OR Penthiobarbital[tiab] OR Pentobarbit*[tiab] OR Pentothal[tiab] OR Pentymal[tiab] OR Phenemal[tiab] OR Phenobarbit*[tiab] OR Phenylbarbital[tiab] OR Phenylethylbarbituric[tiab] OR Placidel[tiab] OR Primaclone[tiab] OR Primidon*[tiab] OR Probarbital[tiab] OR Prominal[tiab] OR Propallylonal[tiab] OR Proxibarbal[tiab] OR Quinalbarbitone[tiab] OR Resimatil[tiab] OR Sagatal[tiab] OR Sebar[tiab] OR Secbutabarbital[tiab] OR Secobarbital[tiab] OR Seconal[tiab] OR Sertan[tiab] OR Sodipental[tiab] OR Surital[tiab] OR Talbutal[tiab] OR Thiamylal[tiab] OR Thiobarbit*[tiab] OR Thiobutabarbital[tiab] OR Thiomebumal[tiab] OR Thionembutal[tiab] OR Thiopent*[tiab] OR Thioquinalbarbitone[tiab] OR Tiobarbital[tiab] OR Transital[tiab] OR Trapanal[tiab] OR Veronal[tiab] OR Vinbarbital[tiab] OR Vinylbital[tiab]) AND ("Clinical Trials as Topic"[Majr] OR "Controlled Clinical Trials as Topic"[Majr] OR "Cross-Over Studies"[Mesh] OR "Double-Blind Method"[Mesh] OR "Pragmatic Clinical Trials as Topic"[Majr] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Single-Blind Method"[Mesh] OR Randomized Controlled Trial[pt] OR Controlled Clinical Trial[pt] OR Pragmatic Clinical Trial[pt] OR Random*[tiab] OR Placebo*[tiab] OR Trial*[tiab] OR Groups[tiab] OR Factorial*[tiab] OR Crossover*[tiab] OR "Cross Over"[tiab] OR "Single Blind"[tiab] OR "Double Blind"[tiab] OR "Triple Blind"[tiab]) NOT MEDLINE[sb]

G. WHO ICTRP

(Schizophrenia OR Schizoaffective OR Schizo Affective OR Schizophreniform OR Schizotypal OR Schizotypy OR Psychosis OR Psychotic OR Paranoid OR Delusional) in the Condition
(Barbiturate OR Barbiturates OR Amobarbital OR Barbital OR Hexobarbital OR Mephobarbital OR Methohexital OR Murexide OR Pentobarbital OR Phenobarbital OR Primidone OR Secobarbital OR Thiamylal OR Thiobarbiturates OR Thiopental) in the Intervention
Recruitment status is ALL

3. Electronic search strategy for benzodiazepines

A. ClinicalTrials.Gov

Condition or Disease: Schizophrenia OR Schizoaffective OR "Schizo Affective" OR Schizophreniform OR Schizotypal OR Schizotypy OR Psychosis OR Psychotic OR Paranoid OR Delusional
Study Type: Interventional Studies (Clinical Trials)
Intervention/Treatment: Benzodiazepine OR Benzodiazepines OR Alprazolam OR Bromazepam OR Clonazepam OR Diazepam OR Chlordiazepoxide OR Midazolam OR Triazolam OR Flurazepam OR Lorazepam OR Nitrazepam OR Oxazepam OR Temazepam
First Posted: From 01/01/2010 To 01/08/2018

B. Cochrane Central Register of Controlled Trials

([mh Schizophrenia] or [mh "Schizophrenia, Childhood"] or [mh "Schizotypal Personality Disorder"] or [mh ^"Psychotic Disorders"] or [mh "Paranoid Disorders"] or (Delusional Disorder* or Psychotic* or Psychosis or Psychoses or Schizoaffective or "Schizo Affective" or Schizophreniform or Schizotyp* or Schizophreni* or "Dementia Praecox" or Paranoi* or "Folie a Deux" or "Folie a Trois"):ti,ab) and ([mh Benzodiazepines] or ("3 Hydroxydiazepam" or "4306-CB" or "Adinazolam" or "Adumbran" or "AHN 086" or "Alodorm" or "Alprazolam" or "Alprazolan" or "Alprox" or "Antelepsin" or "Anthramycin" or "Antramycin" or "Anxyrex" or "Apaurin" or "Apo Alpraz" or "Apo Triazo" or "Ativan" or Benzodiazepin* or "Bretazenil" or "Ro 16-6028" or "BromaLich" or "Bromaz 1A Pharma" or "Bromazanil" or "Bromazep Von Ct" or "Bromazepam" or "Calmday" or "Camazepam" or "B 5833" or "S-58-33" or "SB 5833" or "Cassadan" or "Centrax" or "Chlorazepate" or "Chlordiazepoxide" or "Chlozepid" or "Clobazam" or "HR 376" or "Onfi" or "LM-2717" or "Frisium" or "Urbanyl" or "Clonazepam" or "Clorazepate" or "D 65MT" or "D40TA" or "D-40TA" or "D65MT" or "Dalmadorm" or "Dalmane" or "Dasuen" or "Dealkylprazepam" or "Delorazepam" or "Chlordesmethyldiazepam" or "Chlorodesmethyldiazepam" or "Chloronordiazepam" or "Chlordemethyldiazepam" or "Demethyldiazepam" or "Demetrin" or "Deoxydemoxepam" or "Desmethyldiazepam" or "Devazepide" or "Diazemuls" or "Diazepam" or "Dikaliumclorazepat" or "Donix" or "Dormalon" or "Dormicum" or "Dormodor" or "Dormo-Puren" or "Duralozam" or "Durazanil" or "Durazolam" or "Eatan" or "Elenium" or "Esparon" or "Estazolam" or "Euhypnos" or "Faustan" or "Flumazenil" or "Flumazepil" or "Fluni 1A Pharma" or "Flunibeta" or "Flunimerck" or "Fluninoc" or "Flunitrazepam" or "Flunizep Von Ct" or "Flurazepam" or "Fluridrazepam" or "Flutazolam" or "MS 4101" or "Gastrotsepin" or "Gastrozepin" or "Girisopam" or "EGIS 5810" or "GYKI 51189" or "Halcion" or "Hydroxydiazepam" or "Idalprem" or "Imadorm" or "Imeson" or "Imidazenil" or "Kalma" or "KC 5944" or "L 364,718" or "L 365260" or "L 365,260" or "L 365346" or "L364,718" or "Lanexat" or "Laubeel" or "Levanxol" or "Lexatin" or "Lexomil" or "Lexotan" or "Lexotanil" or "Librium" or "Lorazep Von Ct" or "Lorazepam" or "LS 519" or "L-S 519" or "LS519" or "Lysanxia" or "Medazepam" or "Metaclazepam" or "Ka 2527" or "Methaminodiazepoxide" or "Methyloxazepam" or "Midazolam" or "MK 329" or "MK329" or "Mogadon" or "N Desalkylhalazepam" or "N Descyclopropylmethyl Prazepam" or "N Descyclopropylmethylprazepam" or "N Destrifluoroethylhalazepam" or "Narcozep" or "Nerisopam" or "GYKI 52322" or "GYKI 52 322" or "GYKI-522322" or "Nitrazadon" or "Nitrazep" or "Nitrazepam" or "Nitrodiazepam" or "Nobrium" or "Nocturne" or "Nordaz" or "Nordazepam" or "Nordiazepam" or "NorkotralTema" or "Normison" or "Normitab" or "Norprazepam" or "Nortem" or "Novanox" or "Novo Alprazol" or "Novo Lorazem" or "Nu Alpraz" or "Nu Loraz" or "Nuctalon" or "Orfidal Wyeth" or "Oxazepam" or "Oxydiazepam" or "Pinazepam" or "Propazepam" or "Domar" or "Z-905" or "Duna" or "PirenBasan" or Pirenzepin* or "Planum" or "Prazepam" or "Pronervon T" or "ProSom" or "Pyrenzepine" or "Quazepam" or "Quiedorm" or "Doral" or "Sch 16134" or "Radedorm" or "Ralozam" or "Reapam" or "Relanium" or "Remestan" or "Remnos" or "Restoril" or "Rivotril" or "Ro 15 1788" or "Ro 151788" or "Ro 15-4513" or "Ro15-4513" or "RO-154513" or "Ro 21 3981" or "Ro 213981" or "Ro 5 2180" or "Ro 5 4556" or "Ro 5 5345" or "Ro 52180" or "Ro 53350" or "Ro 5-3350" or "Ro 54023" or "Ro 5-4023" or "Ro 54556" or "Ro 5-4864" or "Ro5-4864" or "Ro-05-4864" or "Chlordiazepam" or "RO54200" or "RO-5-4200" or "Ro55345" or "Rohipnol" or "Rohypnol" or "Romazicon" or "Rudotel" or "Rusedal" or "SaH 47 603" or "SaH 47603" or "Sarmazenil" or "Sedicepan" or "Seduxen" or "Serax" or "Serenade" or "Sibazon" or "Signopam" or "Sinestron" or "Somagerol" or "Somnite" or "Staurodorm" or "Stesolid" or "Tafil" or "Tasedan" or "Tazepam" or "Temaze" or "Temazep Von Ct" or "Temazepam" or "Temesta" or "Temtabs" or "Tenox" or "Timelotem" or "Tofisopam" or "Tofizopam" or "Levotofisopam" or "Dextofisopam" or "EGYT-341" or "Grandaxin" or "Tolid" or "Trankimazin" or "Tranxene" or "Tranxilium" or "Tranxilium N" or "Triazolam" or "Trilam" or "U 33,030" or "U31,889" or "U-31,889" or "U33,030" or "Ulcoprotect" or "Ulgescum" or "Valium" or "Vegesan" or "Versed" or "WY 3917" or "WY 4036" or "WY3917" or "WY4036" or "Xanax"):ti,ab) Publication Year from 2010, in Trials

C. EMBASE

1. Exp Schizophrenia/ OR Exp Schizophrenia Spectrum Disorder/ OR Schizophreniform Disorder/ OR Schizotypal Personality Disorder/ OR Psychosis/ OR Exp Paranoid Psychosis/ OR Brief Psychotic Disorder/ OR Delusional Disorder/ OR Schizoaffective Psychosis/ OR (Delusional Disorder* OR Psychotic* OR Psychosis OR Psychoses OR Schizoaffective OR "Schizo Affective" OR Schizophreniform OR Schizotyp* or Schizophreni* OR "Dementia Praecox" OR Paranoi* OR "Folie a Deux" OR "Folie a Trois").ti,ab.

2. Exp Benzodiazepine Derivative/ OR ("3 Hydroxydiazepam" OR "4306-CB" OR "Adinazolam" OR "Adumbran" OR "AHN 086" OR "Alodorm" OR "Alprazolam" OR "Alprazolan" OR "Alprox" OR "Antelepsin" OR "Anthramycin" OR "Antramycin" OR "Anxyrex" OR "Apaurin" OR "Apo Alpraz" OR "Apo Triazo" OR "Ativan" OR Benzodiazepin* OR "Bretazenil" OR "Ro 16-6028" OR "BromaLich" OR "Bromaz 1A Pharma" OR "Bromazanil" OR "Bromazep Von Ct" OR "Bromazepam" OR "Calmday" OR "Camazepam" OR "B 5833" OR "S-58-33" OR "SB 5833" OR "Cassadan" OR "Centrax" OR "Chlorazepate" OR "Chlordiazepoxide" OR "Chlozepid" OR "Clobazam" OR "HR 376" OR "Onfi" OR "LM-2717" OR "Frisium" OR "Urbanyl" OR "Clonazepam" OR "Clorazepate" OR "D 65MT" OR "D40TA" OR "D-40TA" OR "D65MT" OR "Dalmadorm" OR "Dalmane" OR "Dasuen" OR "Dealkylprazepam" OR "Delorazepam" OR "Chlordesmethyldiazepam" OR "Chlorodesmethyldiazepam" OR "Chloronordiazepam" OR "Chlordemethyldiazepam" OR "Demethyldiazepam" OR "Demetrin" OR "Deoxydemoxepam" OR "Desmethyldiazepam" OR "Devazepide" OR "Diazemuls" OR "Diazepam" OR "Dikaliumclorazepat" OR "Donix" OR "Dormalon" OR "Dormicum" OR "Dormodor" OR "Dormo-Puren" OR "Duralozam" OR "Durazanil" OR "Durazolam" OR "Eatan" OR "Elenium" OR "Esparon" OR "Estazolam" OR "Euhypnos" OR "Faustan" OR "Flumazenil" OR "Flumazepil" OR "Fluni 1A Pharma" OR "Flunibeta" OR "Flunimerck" OR "Fluninoc" OR "Flunitrazepam" OR "Flunizep Von Ct" OR "Flurazepam" OR "Fluridrazepam" OR "Flutazolam" OR "MS 4101" OR "Gastrotsepin" OR "Gastrozepin" OR "Girisopam" OR "EGIS 5810" OR "GYKI 51189" OR "Halcion" OR "Hydroxydiazepam" OR "Idalprem" OR "Imadorm" OR "Imeson" OR "Imidazenil" OR "Kalma" OR "KC 5944" OR "L 364,718" OR "L 365260" OR "L 365,260" OR "L 365346" OR "L364,718" OR "Lanexat" OR "Laubeel" OR "Levanxol" OR "Lexatin" OR "Lexomil" OR "Lexotan" OR "Lexotanil" OR "Librium" OR "Lorazep Von Ct" OR "Lorazepam" OR "LS 519" OR "L-S 519" OR "LS519" OR "Lysanxia" OR "Medazepam" OR "Metaclazepam" OR "Ka 2527" OR "Methaminodiazepoxide" OR "Methyloxazepam" OR "Midazolam" OR "MK 329" OR "MK329" OR "Mogadon" OR "N Desalkylhalazepam" OR "N Descyclopropylmethyl Prazepam" OR "N Descyclopropylmethylprazepam" OR "N Destrifluoroethylhalazepam" OR "Narcozep" OR "Nerisopam" OR "GYKI 52322" OR "GYKI 52 322" OR "GYKI-522322" OR "Nitrazadon" OR "Nitrazep" OR "Nitrazepam" OR "Nitrodiazepam" OR "Nobrium" OR "Nocturne" OR "Nordaz" OR "Nordazepam" OR "Nordiazepam" OR "NorkotralTema" OR "Normison" OR "Normitab" OR "Norprazepam" OR "Nortem" OR "Novanox" OR "Novo Alprazol" OR "Novo Lorazem" OR "Nu Alpraz" OR "Nu Loraz" OR "Nuctalon" OR "Orfidal Wyeth" OR "Oxazepam" OR "Oxydiazepam" OR "Pinazepam" OR "Propazepam" OR "Domar" OR "Z-905" OR "Duna" OR "PirenBasan" OR Pirenzepin* OR "Planum" OR "Prazepam" OR "Pronervon T" OR "ProSom" OR "Pyrenzepine" OR "Quazepam" OR "Quiedorm" OR "Doral" OR "Sch 16134" OR "Radedorm" OR "Ralozam" OR "Reapam" OR "Relanium" OR "Remestan" OR "Remnos" OR "Restoril" OR "Rivotril" OR "Ro 15 1788" OR "Ro 151788" OR "Ro 15-4513" OR "Ro15-4513" OR "RO-154513" OR "Ro 21 3981" OR "Ro 213981" OR "Ro 5 2180" OR "Ro 5 4556" OR "Ro 5 5345" OR "Ro 52180" OR "Ro 53350" OR "Ro 5-3350" OR "Ro 54023" OR "Ro 5-4023" OR "Ro 54556" OR "Ro 5-4864" OR "Ro5-4864" OR "Ro-05-4864" OR "Chlordiazepam" OR "RO54200" OR "RO-5-4200" OR "Ro55345" OR "Rohipnol" OR "Rohypnol" OR "Romazicon" OR "Rudotel" OR "Rusedal" OR "SaH 47 603" OR "SaH 47603" OR "Sarmazenil" OR "Sedicepan" OR "Seduxen" OR "Serax" OR "Serenade" OR "Sibazon" OR "Signopam" OR "Sinestron" OR "Somagerol" OR "Somnite" OR "Staurodorm" OR "Stesolid" OR "Tafil" OR "Tasedan" OR "Tazepam" OR "Temaze" OR "Temazep Von Ct" OR "Temazepam" OR "Temesta" OR "Temtabs" OR "Tenox" OR "Timelotem" OR "Tofisopam" OR "Tofizopam" OR "Levotofisopam" OR "Dextofisopam" OR "EGYT-341" OR "Grandaxin" OR "Tolid" OR "Trankimazin" OR "Tranxene" OR "Tranxilium" OR "Tranxilium N" OR "Triazolam" OR "Trilam" OR "U 33,030" OR "U31,889" OR "U-31,889" OR "U33,030" OR "Ulcoprotect" OR "Ulgescum" OR "Valium" OR "Vegesan" OR "Versed" OR "WY 3917" OR "WY 4036" OR "WY3917" OR "WY4036" OR "Xanax").ti,ab.
3. Randomization/ OR Crossover-Procedure/ OR Double-Blind Procedure/ OR Randomized Controlled Trial/ OR Single-Blind Procedure/ OR (Random* OR Factorial* OR Crossover* OR Cross Over* OR Placebo* OR ((Singl* OR Doubl* OR Trebl* or Tripl*) adj (Mask* OR Blind*)) OR Assign* OR Allocat* OR Volunteer* OR Groups OR Trial*).mp.
4. 1 AND 2 AND 3
5. Exp Animals/ OR Exp Invertebrate/ OR Animal Experiment/ OR Animal Model/ OR Animal Tissue/ OR Animal Cell/ OR Nonhuman/
6. Human/ OR Normal Human/ OR Human Cell/
7. 5 AND 6
8. 5 NOT 7
9. 4 NOT 8
10. Limit 9 to YR="2010 -Current"
11. Limit 10 to MEDLINE
12. 10 NOT 11
13. Limit 12 to EMBASE
14. Limit 13 to Exclude MEDLINE Journals

D. MEDLINE

1. Exp Schizophrenia/ OR Schizophrenia, Childhood/ OR Schizotypal Personality Disorder/ OR Psychotic Disorders/ OR Paranoid Disorders/ OR (Delusional Disorder* OR Psychotic* OR Psychosis OR Psychoses OR Schizoaffective OR "Schizo Affective" OR Schizophreniform OR Schizotyp* or Schizophreni* OR "Dementia Praecox" OR Paranoi* OR "Folie a Deux" OR "Folie a Trois").ti,ab.
2. Exp Benzodiazepines/ OR ("3 Hydroxydiazepam" OR "4306-CB" OR "Adinazolam" OR "Adumbran" OR "AHN 086" OR "Alodorm" OR "Alprazolam" OR "Alprazolan" OR "Alprox" OR "Antelepsin" OR "Anthramycin" OR "Antramycin" OR "Anxyrex" OR "Apaurin" OR "Apo Alpraz" OR "Apo Triazo" OR "Ativan" OR Benzodiazepin* OR "Bretazenil" OR "Ro 16-6028" OR "BromaLich" OR "Bromaz 1A Pharma" OR "Bromazanil" OR "Bromazep Von Ct" OR "Bromazepam" OR "Calmday" OR "Camazepam" OR "B 5833" OR "S-58-33" OR "SB 5833" OR "Cassadan" OR "Centrax" OR "Chlorazepate" OR "Chlordiazepoxide" OR "Chlozepid" OR "Clobazam" OR "HR 376" OR "Onfi" OR "LM-2717" OR "Frisium" OR "Urbanyl" OR "Clonazepam" OR "Clorazepate" OR "D 65MT" OR "D40TA" OR "D-40TA" OR "D65MT" OR "Dalmadorm" OR "Dalmane" OR "Dasuen" OR "Dealkylprazepam" OR "Delorazepam" OR "Chlordesmethyldiazepam" OR "Chlorodesmethyldiazepam" OR "Chloronordiazepam" OR "Chlordemethyldiazepam" OR "Demethyldiazepam" OR "Demetrin" OR "Deoxydemoxepam" OR "Desmethyldiazepam" OR "Devazepide" OR "Diazemuls" OR "Diazepam" OR "Dikaliumclorazepat" OR "Donix" OR "Dormalon" OR "Dormicum" OR "Dormodor" OR "Dormo-Puren" OR "Duralozam" OR "Durazanil" OR "Durazolam" OR "Eatan" OR "Elenium" OR "Esparon" OR "Estazolam" OR "Euhypnos" OR "Faustan" OR "Flumazenil" OR "Flumazepil" OR "Fluni 1A Pharma" OR "Flunibeta" OR "Flunimerck" OR "Fluninoc" OR "Flunitrazepam" OR "Flunizep Von Ct" OR "Flurazepam" OR "Fluridrazepam" OR "Flutazolam" OR "MS 4101" OR "Gastrotsepin" OR "Gastrozepin" OR "Girisopam" OR "EGIS 5810" OR "GYKI 51189" OR "Halcion" OR "Hydroxydiazepam" OR "Idalprem" OR "Imadorm" OR "Imeson" OR "Imidazenil" OR "Kalma" OR "KC 5944" OR "L 364,718" OR "L 365260" OR "L 365,260" OR "L 365346" OR "L364,718" OR "Lanexat" OR "Laubeel" OR "Levanxol" OR "Lexatin" OR "Lexomil" OR "Lexotan" OR "Lexotanil" OR "Librium" OR "Lorazep Von Ct" OR "Lorazepam" OR "LS 519" OR "L-S 519" OR "LS519" OR "Lysanxia" OR "Medazepam" OR "Metaclazepam" OR "Ka 2527" OR "Methaminodiazepoxide" OR "Methyloxazepam" OR "Midazolam" OR "MK 329" OR "MK329" OR "Mogadon" OR "N Desalkylhalazepam" OR "N Descyclopropylmethyl Prazepam" OR "N Descyclopropylmethylprazepam" OR "N Destrifluoroethylhalazepam" OR "Narcozep" OR "Nerisopam" OR "GYKI 52322" OR "GYKI 52 322" OR "GYKI-522322" OR "Nitrazadon" OR "Nitrazep" OR "Nitrazepam" OR "Nitrodiazepam" OR "Nobrium" OR "Nocturne" OR "Nordaz" OR "Nordazepam" OR "Nordiazepam" OR "NorkotralTema" OR "Normison" OR "Normitab" OR "Norprazepam" OR "Nortem" OR "Novanox" OR "Novo Alprazol" OR "Novo Lorazem" OR "Nu Alpraz" OR "Nu Loraz" OR "Nuctalon" OR "Orfidal Wyeth" OR "Oxazepam" OR "Oxydiazepam" OR "Pinazepam" OR "Propazepam" OR "Domar" OR "Z-905" OR "Duna" OR "PirenBasan" OR Pirenzepin* OR "Planum" OR "Prazepam" OR "Pronervon T" OR "ProSom" OR "Pyrenzepine" OR "Quazepam" OR "Quiedorm" OR "Doral" OR "Sch 16134" OR "Radedorm" OR "Ralozam" OR "Reapam" OR "Relanium" OR "Remestan" OR "Remnos" OR "Restoril" OR "Rivotril" OR "Ro 15 1788" OR "Ro 151788" OR "Ro 15-4513" OR "Ro15-4513" OR "RO-154513" OR "Ro 21 3981" OR "Ro 213981" OR "Ro 5 2180" OR "Ro 5 4556" OR "Ro 5 5345" OR "Ro 52180" OR "Ro 53350" OR "Ro 5-3350" OR "Ro 54023" OR "Ro 5-4023" OR "Ro 54556" OR "Ro 5-4864" OR "Ro5-4864" OR "Ro-05-4864" OR "Chlordiazepam" OR "RO54200" OR "RO-5-4200" OR "Ro55345" OR "Rohipnol" OR "Rohypnol" OR "Romazicon" OR "Rudotel" OR "Rusedal" OR "SaH 47 603" OR "SaH 47603" OR "Sarmazenil" OR "Sedicepan" OR "Seduxen" OR "Serax" OR "Serenade" OR "Sibazon" OR "Signopam" OR "Sinestron" OR "Somagerol" OR "Somnite" OR "Staurodorm" OR "Stesolid" OR "Tafil" OR "Tasedan" OR "Tazepam" OR "Temaze" OR "Temazep Von Ct" OR "Temazepam" OR "Temesta" OR "Temtabs" OR "Tenox" OR "Timelotem" OR "Tofisopam" OR "Tofizopam" OR "Levotofisopam" OR "Dextofisopam" OR "EGYT-341" OR "Grandaxin" OR "Tolid" OR "Trankimazin" OR "Tranxene" OR "Tranxilium" OR "Tranxilium N" OR "Triazolam" OR "Trilam" OR "U 33,030" OR "U31,889" OR "U-31,889" OR "U33,030" OR "Ulcoprotect" OR "Ulgescum" OR "Valium" OR "Vegesan" OR "Versed" OR "WY 3917" OR "WY 4036" OR "WY3917" OR "WY4036" OR "Xanax").ti,ab.
3. Clinical Trials as Topic/ OR Controlled Clinical Trials as Topic/ OR Cross-Over Studies/ OR Double-Blind Method/ OR Exp Randomized Controlled Trials as Topic/ OR Pragmatic Clinical Trials as Topic/ OR Single-Blind Method/ OR (Clinical Trial OR Randomized Controlled Trial OR Controlled Clinical Trial OR Pragmatic Clinical Trial).pt. OR (Random* OR Factorial* OR Crossover* OR Cross Over* OR Placebo* OR ((Singl* OR Doubl* OR Trebl* or Tripl*) adj (Mask* OR Blind*)) OR Assign* OR Allocat* OR Volunteer* OR Groups OR Trial*).mp. OR Drug Therapy.fs. NOT (Animals NOT (Humans and Animals)).sh.
4. 1 AND 2 AND 3
5. Limit 4 to YR="2010 -Current"

E. PsycINFO

1. Exp Schizophrenia/ OR Schizotypal Personality Disorder/ OR Schizotypy/ OR Schizoaffective Disorder/ OR Schizophreniform Disorder/ OR Paranoid Schizophrenia/ OR Psychosis/ OR "Paranoia (Psychosis)"/ OR

(Delusional Disorder* OR Psychotic* OR Psychosis OR Psychoses OR Schizoaffective OR "Schizo Affective" OR Schizophreniform OR Schizotyp* or Schizophreni* OR "Dementia Praecox" OR Paranoi* OR "Folie a Deux" OR "Folie a Trois").ti,ab.

2. Exp Benzodiazepines/ OR ("3 Hydroxydiazepam" OR "4306-CB" OR "Adinazolam" OR "Adumbran" OR "AHN 086" OR "Alodorm" OR "Alprazolam" OR "Alprazolan" OR "Alprox" OR "Antelepsin" OR "Anthramycin" OR "Antramycin" OR "Anxyrex" OR "Apaurin" OR "Apo Alpraz" OR "Apo Triazo" OR "Ativan" OR Benzodiazepin* OR "Bretazenil" OR "Ro 16-6028" OR "BromaLich" OR "Bromaz 1A Pharma" OR "Bromazanil" OR "Bromazep Von Ct" OR "Bromazepam" OR "Calmday" OR "Camazepam" OR "B 5833" OR "S-58-33" OR "SB 5833" OR "Cassadan" OR "Centrax" OR "Chlorazepate" OR "Chlordiazepoxide" OR "Chlozepid" OR "Clobazam" OR "HR 376" OR "Onfi" OR "LM-2717" OR "Frisium" OR "Urbanyl" OR "Clonazepam" OR "Clorazepate" OR "D 65MT" OR "D40TA" OR "D-40TA" OR "D65MT" OR "Dalmadorm" OR "Dalmane" OR "Dasuen" OR "Dealkylprazepam" OR "Delorazepam" OR "Chlordesmethyldiazepam" OR "Chlorodesmethyldiazepam" OR "Chloronordiazepam" OR "Chlordemethyldiazepam" OR "Demethyldiazepam" OR "Demetrin" OR "Deoxydemoxepam" OR "Desmethyldiazepam" OR "Devazepide" OR "Diazemuls" OR "Diazepam" OR "Dikaliumclorazepat" OR "Donix" OR "Dormalon" OR "Dormicum" OR "Dormodor" OR "Dormo-Puren" OR "Duralozam" OR "Durazanil" OR "Durazolam" OR "Eatan" OR "Elenium" OR "Esparon" OR "Estazolam" OR "Euhypnos" OR "Faustan" OR "Flumazenil" OR "Flumazepil" OR "Fluni 1A Pharma" OR "Flunibeta" OR "Flunimerck" OR "Fluninoc" OR "Flunitrazepam" OR "Flunizep Von Ct" OR "Flurazepam" OR "Fluridrazepam" OR "Flutazolam" OR "MS 4101" OR "Gastrotsepin" OR "Gastrozepin" OR "Girisopam" OR "EGIS 5810" OR "GYKI 51189" OR "Halcion" OR "Hydroxydiazepam" OR "Idalprem" OR "Imadorm" OR "Imeson" OR "Imidazenil" OR "Kalma" OR "KC 5944" OR "L 364,718" OR "L 365260" OR "L 365,260" OR "L 365346" OR "L364,718" OR "Lanexat" OR "Laubeel" OR "Levanxol" OR "Lexatin" OR "Lexomil" OR "Lexotan" OR "Lexotanil" OR "Librium" OR "Lorazep Von Ct" OR "Lorazepam" OR "LS 519" OR "L-S 519" OR "LS519" OR "Lysanxia" OR "Medazepam" OR "Metaclazepam" OR "Ka 2527" OR "Methaminodiazepoxide" OR "Methyloxazepam" OR "Midazolam" OR "MK 329" OR "MK329" OR "Mogadon" OR "N Desalkylhalazepam" OR "N Descyclopropylmethyl Prazepam" OR "N Descyclopropylmethylprazepam" OR "N Destrifluoroethylhalazepam" OR "Narcozep" OR "Nerisopam" OR "GYKI 52322" OR "GYKI 52 322" OR "GYKI-522322" OR "Nitrazadon" OR "Nitrazep" OR "Nitrazepam" OR "Nitrodiazepam" OR "Nobrium" OR "Nocturne" OR "Nordaz" OR "Nordazepam" OR "Nordiazepam" OR "NorkotralTema" OR "Normison" OR "Normitab" OR "Norprazepam" OR "Nortem" OR "Novanox" OR "Novo Alprazol" OR "Novo Lorazem" OR "Nu Alpraz" OR "Nu Loraz" OR "Nuctalon" OR "Orfidal Wyeth" OR "Oxazepam" OR "Oxydiazepam" OR "Pinazepam" OR "Propazepam" OR "Domar" OR "Z-905" OR "Duna" OR "PirenBasan" OR Pirenzepin* OR "Planum" OR "Prazepam" OR "Pronervon T" OR "ProSom" OR "Pyrenzepine" OR "Quazepam" OR "Quiedorm" OR "Doral" OR "Sch 16134" OR "Radedorm" OR "Ralozam" OR "Reapam" OR "Relanium" OR "Remestan" OR "Remnos" OR "Restoril" OR "Rivotril" OR "Ro 15 1788" OR "Ro 151788" OR "Ro 15-4513" OR "Ro15-4513" OR "RO-154513" OR "Ro 21 3981" OR "Ro 213981" OR "Ro 5 2180" OR "Ro 5 4556" OR "Ro 5 5345" OR "Ro 52180" OR "Ro 53350" OR "Ro 5-3350" OR "Ro 54023" OR "Ro 5-4023" OR "Ro 54556" OR "Ro 5-4864" OR "Ro5-4864" OR "Ro-05-4864" OR "Chlordiazepam" OR "RO54200" OR "RO-5-4200" OR "Ro55345" OR "Rohipnol" OR "Rohypnol" OR "Romazicon" OR "Rudotel" OR "Rusedal" OR "SaH 47 603" OR "SaH 47603" OR "Sarmazenil" OR "Sedicepan" OR "Seduxen" OR "Serax" OR "Serenade" OR "Sibazon" OR "Signopam" OR "Sinestron" OR "Somagerol" OR "Somnite" OR "Staurodorm" OR "Stesolid" OR "Tafil" OR "Tasedan" OR "Tazepam" OR "Temaze" OR "Temazep Von Ct" OR "Temazepam" OR "Temesta" OR "Temtabs" OR "Tenox" OR "Timelotem" OR "Tofisopam" OR "Tofizopam" OR "Levotofisopam" OR "Dextofisopam" OR "EGYT-341" OR "Grandaxin" OR "Tolid" OR "Trankimazin" OR "Tranxene" OR "Tranxilium" OR "Tranxilium N" OR "Triazolam" OR "Trilam" OR "U 33,030" OR "U31,889" OR "U-31,889" OR "U33,030" OR "Ulcoprotect" OR "Ulgescum" OR "Valium" OR "Vegesan" OR "Versed" OR "WY 3917" OR "WY 4036" OR "WY3917" OR "WY4036" OR "Xanax").ti,ab.
3. Exp Treatment Effectiveness Evaluation/ OR Mental Health Program Evaluation/ OR Placebo/ OR (Random* OR Factorial* OR Crossover* OR Cross Over* OR Placebo* OR ((Singl* OR Doubl* OR Trebl* or Tripl*) adj (Mask* OR Blind*)) OR Assign* OR Allocat* OR Volunteer* OR Groups OR Trial*).mp.
4. 1 AND 2 AND 3
5. Limit 4 to YR="2010 -Current"

F. PubMed

("Schizophrenia"[Mesh] OR "Schizophrenia, Childhood"[Mesh] OR "Schizotypal Personality Disorder"[Mesh] OR "Psychotic Disorders"[Mesh:NoExp] OR "Paranoid Disorders"[Mesh] OR Delusional Disorder*[tiab] OR Psychotic*[tiab] OR Psychosis[tiab] OR Psychoses[tiab] OR Schizoaffective[tiab] OR "Schizo Affective"[tiab] OR Schizophreniform[tiab] OR Schizotyp*[tiab] or Schizophreni*[tiab] OR "Dementia Praecox"[tiab] OR Paranoi*[tiab] OR "Folie a Deux"[tiab] OR "Folie a Trois"[tiab]) AND ("Benzodiazepines"[Mesh] OR "3 Hydroxydiazepam"[tiab] OR "4306-CB"[tiab] OR "Adinazolam"[tiab] OR "Adumbran"[tiab] OR "AHN 086"[tiab] OR "Alodorm"[tiab] OR "Alprazolam"[tiab] OR "Alprazolan"[tiab] OR "Alprox"[tiab] OR

"Antelepsin"[tiab] OR "Anthramycin"[tiab] OR "Antramycin"[tiab] OR "Anxyrex"[tiab] OR "Apaurin"[tiab] OR "Apo Alpraz"[tiab] OR "Apo Triazo"[tiab] OR "Ativan"[tiab] OR Benzodiazepin*[tiab] OR "Bretazenil"[tiab] OR "Ro 16-6028"[tiab] OR "BromaLich"[tiab] OR "Bromaz 1A Pharma"[tiab] OR "Bromazanil"[tiab] OR "Bromazep Von Ct"[tiab] OR "Bromazepam"[tiab] OR "Calmday"[tiab] OR "Camazepam"[tiab] OR "B 5833"[tiab] OR "S-58-33"[tiab] OR "SB 5833"[tiab] OR "Cassadan"[tiab] OR "Centrax"[tiab] OR "Chlorazepate"[tiab] OR "Chlordiazepoxide"[tiab] OR "Chlozepid"[tiab] OR "Clobazam"[tiab] OR "HR 376"[tiab] OR "Onfi"[tiab] OR "LM-2717"[tiab] OR "Frisium"[tiab] OR "Urbanyl"[tiab] OR "Clonazepam"[tiab] OR "Clorazepate"[tiab] OR "D 65MT"[tiab] OR "D40TA"[tiab] OR "D-40TA"[tiab] OR "D65MT"[tiab] OR "Dalmadorm"[tiab] OR "Dalmane"[tiab] OR "Dasuen"[tiab] OR "Dealkylprazepam"[tiab] OR "Delorazepam"[tiab] OR "Chlordesmethyldiazepam"[tiab] OR "Chlorodesmethyldiazepam"[tiab] OR "Chloronordiazepam"[tiab] OR "Chlordemethyldiazepam"[tiab] OR "Demethyldiazepam"[tiab] OR "Demetrin"[tiab] OR "Deoxydemoxepam"[tiab] OR "Desmethyldiazepam"[tiab] OR "Devazepide"[tiab] OR "Diazemuls"[tiab] OR "Diazepam"[tiab] OR "Dikaliumclorazepat"[tiab] OR "Donix"[tiab] OR "Dormalon"[tiab] OR "Dormicum"[tiab] OR "Dormodor"[tiab] OR "Dormo-Puren"[tiab] OR "Duralozam"[tiab] OR "Durazanil"[tiab] OR "Durazolam"[tiab] OR "Eatan"[tiab] OR "Elenium"[tiab] OR "Esparon"[tiab] OR "Estazolam"[tiab] OR "Euhypnos"[tiab] OR "Faustan"[tiab] OR "Flumazenil"[tiab] OR "Flumazepil"[tiab] OR "Fluni 1A Pharma"[tiab] OR "Flunibeta"[tiab] OR "Flunimerck"[tiab] OR "Fluninoc"[tiab] OR "Flunitrazepam"[tiab] OR "Flunizep Von Ct"[tiab] OR "Flurazepam"[tiab] OR "Fluridrazepam"[tiab] OR "Flutazolam"[tiab] OR "MS 4101"[tiab] OR "Gastrotsepin"[tiab] OR "Gastrozepin"[tiab] OR "Girisopam"[tiab] OR "EGIS 5810"[tiab] OR "GYKI 51189"[tiab] OR "Halcion"[tiab] OR "Hydroxydiazepam"[tiab] OR "Idalprem"[tiab] OR "Imadorm"[tiab] OR "Imeson"[tiab] OR "Imidazenil"[tiab] OR "Kalma"[tiab] OR "KC 5944"[tiab] OR "L 364,718"[tiab] OR "L 365260"[tiab] OR "L 365,260"[tiab] OR "L 365346"[tiab] OR "L364,718"[tiab] OR "Lanexat"[tiab] OR "Laubeel"[tiab] OR "Levanxol"[tiab] OR "Lexatin"[tiab] OR "Lexomil"[tiab] OR "Lexotan"[tiab] OR "Lexotanil"[tiab] OR "Librium"[tiab] OR "Lorazep Von Ct"[tiab] OR "Lorazepam"[tiab] OR "LS 519"[tiab] OR "L-S 519"[tiab] OR "LS519"[tiab] OR "Lysanxia"[tiab] OR "Medazepam"[tiab] OR "Metaclazepam"[tiab] OR "Ka 2527"[tiab] OR "Methaminodiazepoxide"[tiab] OR "Methyloxazepam"[tiab] OR "Midazolam"[tiab] OR "MK 329"[tiab] OR "MK329"[tiab] OR "Mogadon"[tiab] OR "N Desalkylhalazepam"[tiab] OR "N Descyclopropylmethyl Prazepam"[tiab] OR "N Descyclopropylmethylprazepam"[tiab] OR "N Destrifluoroethylhalazepam"[tiab] OR "Narcozep"[tiab] OR "Nerisopam"[tiab] OR "GYKI 52322"[tiab] OR "GYKI 52 322"[tiab] OR "GYKI-522322"[tiab] OR "Nitrazadon"[tiab] OR "Nitrazep"[tiab] OR "Nitrazepam"[tiab] OR "Nitrodiazepam"[tiab] OR "Nobrium"[tiab] OR "Nocturne"[tiab] OR "Nordaz"[tiab] OR "Nordazepam"[tiab] OR "Nordiazepam"[tiab] OR "NorkotralTema"[tiab] OR "Normison"[tiab] OR "Normitab"[tiab] OR "Norprazepam"[tiab] OR "Nortem"[tiab] OR "Novanox"[tiab] OR "Novo Alprazol"[tiab] OR "Novo Lorazem"[tiab] OR "Nu Alpraz"[tiab] OR "Nu Loraz"[tiab] OR "Nuctalon"[tiab] OR "Orfidal Wyeth"[tiab] OR "Oxazepam"[tiab] OR "Oxydiazepam"[tiab] OR "Pinazepam"[tiab] OR "Propazepam"[tiab] OR "Domar"[tiab] OR "Z-905"[tiab] OR "Duna"[tiab] OR "PirenBasan"[tiab] OR Pirenzepin*[tiab] OR "Planum"[tiab] OR "Prazepam"[tiab] OR "Pronervon T"[tiab] OR "ProSom"[tiab] OR "Pyrenzepine"[tiab] OR "Quazepam"[tiab] OR "Quiedorm"[tiab] OR "Doral"[tiab] OR "Sch 16134"[tiab] OR "Radedorm"[tiab] OR "Ralozam"[tiab] OR "Reapam"[tiab] OR "Relanium"[tiab] OR "Remestan"[tiab] OR "Remnos"[tiab] OR "Restoril"[tiab] OR "Rivotril"[tiab] OR "Ro 15 1788"[tiab] OR "Ro 151788"[tiab] OR "Ro 15-4513"[tiab] OR "Ro15-4513"[tiab] OR "RO-154513"[tiab] OR "Ro 21 3981"[tiab] OR "Ro 213981"[tiab] OR "Ro 5 2180"[tiab] OR "Ro 5 4556"[tiab] OR "Ro 5 5345"[tiab] OR "Ro 52180"[tiab] OR "Ro 53350"[tiab] OR "Ro 5-3350"[tiab] OR "Ro 54023"[tiab] OR "Ro 5-4023"[tiab] OR "Ro 54556"[tiab] OR "Ro 5-4864"[tiab] OR "Ro5-4864"[tiab] OR "Ro-05-4864"[tiab] OR "Chlordiazepam"[tiab] OR "RO54200"[tiab] OR "RO-5-4200"[tiab] OR "Ro55345"[tiab] OR "Rohipnol"[tiab] OR "Rohypnol"[tiab] OR "Romazicon"[tiab] OR "Rudotel"[tiab] OR "Rusedal"[tiab] OR "SaH 47 603"[tiab] OR "SaH 47603"[tiab] OR "Sarmazenil"[tiab] OR "Sedicepan"[tiab] OR "Seduxen"[tiab] OR "Serax"[tiab] OR "Serenade"[tiab] OR "Sibazon"[tiab] OR "Signopam"[tiab] OR "Sinestron"[tiab] OR "Somagerol"[tiab] OR "Somnite"[tiab] OR "Staurodorm"[tiab] OR "Stesolid"[tiab] OR "Tafil"[tiab] OR "Tasedan"[tiab] OR "Tazepam"[tiab] OR "Temaze"[tiab] OR "Temazep Von Ct"[tiab] OR "Temazepam"[tiab] OR "Temesta"[tiab] OR "Temtabs"[tiab] OR "Tenox"[tiab] OR "Timelotem"[tiab] OR "Tofisopam"[tiab] OR "Tofizopam"[tiab] OR "Levotofisopam"[tiab] OR "Dextofisopam"[tiab] OR "EGYT-341"[tiab] OR "Grandaxin"[tiab] OR "Tolid"[tiab] OR "Trankimazin"[tiab] OR "Tranxene"[tiab] OR "Tranxilium"[tiab] OR "Tranxilium N"[tiab] OR "Triazolam"[tiab] OR "Trilam"[tiab] OR "U 33,030"[tiab] OR "U31,889"[tiab] OR "U-31,889"[tiab] OR "U33,030"[tiab] OR "Ulcoprotect"[tiab] OR "Ulgescum"[tiab] OR "Valium"[tiab] OR "Vegesan"[tiab] OR "Versed"[tiab] OR "WY 3917"[tiab] OR "WY 4036"[tiab] OR "WY3917"[tiab] OR "WY4036"[tiab] OR "Xanax"[tiab]) AND ("Clinical Trials as Topic"[Majr] OR "Controlled Clinical Trials as Topic"[Majr] OR "Cross-Over Studies"[Mesh] OR "Double-Blind Method"[Mesh] OR "Pragmatic Clinical Trials as Topic"[Majr] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Single-Blind Method"[Mesh] OR Randomized Controlled Trial[pt] OR Controlled Clinical Trial[pt] OR Pragmatic Clinical Trial[pt] OR Random*[tiab] OR Placebo*[tiab] OR Trial*[tiab] OR Groups[tiab] OR Factorial*[tiab] OR

Crossover*[tiab] OR "Cross Over"[tiab] OR "Single Blind"[tiab] OR "Double Blind"[tiab] OR "Triple Blind"[tiab]) AND ("2010/01/01"[PDAT] : "3000/12/31"[PDAT]) NOT MEDLINE[sb]

G. WHO ICTRP

(Schizophrenia OR Schizoaffective OR Schizo Affective OR Schizophreniform OR Schizotypal OR Schizotypy OR Psychosis OR Psychotic OR Paranoid OR Delusional) in the Condition
(Benzodiazepine OR Benzodiazepines OR Alprazolam OR Bromazepam OR Clonazepam OR Diazepam OR Chlordiazepoxide OR Midazolam OR Triazolam OR Flurazepam OR Lorazepam OR Nitrazepam OR Oxazepam OR Temazepam) in the Intervention
Recruitment status is ALL
Date of registration is between 01/01/2010 and 08/01/2018

4. References

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Klein, D. F. & Davis, J. M. (1969). *Diagnosis and drug treatment of psychiatric disorders*. Williams & Wilkins: Baltimore.
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Moher, D., Liberati, A., Tetzlaff, J. & Altman, D. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* **6**, e1000097.
Wolkowitz, O. & Pickar, D. (1991). Benzodiazepines in the treatment of schizophrenia: a review and reappraisal. *American Journal of Psychiatry* **148**, 714-26.

eAppendix 4. Characteristics of included and excluded studies

eAppendix 4. Characteristics of included and excluded studies

1. Characteristics of included studies

A. Casey 1960a

Study characteristics		
References	(Bennett, 1959; Casey *et al.*, 1960a)	
Methods	Allocation: randomized; no further details Blindness: double-blind Design: crossover Duration: 12 weeks first crossover phase; shorter-term Washout period: 1 month washout period without placebo for acute and 2 months for chronic patients Dosing schedule: fixed, oral Location: Veteran Administration Hospitals, USA Setting: 37 centers, inpatients Funding: unclear; Smith, Klein & French Laboratories (generously supplied the drugs of the study)	
Participants	Diagnosis: men with schizophrenic reactions who were hospitalized; chronic patients 81% of 805, acute 19% (non-disturbed 73%, disturbed 27%, chronic and non-disturbed 61%) History: average 10 years duration of illness, average 7 years of hospitalization, 65% of patients had received tranquilizers before, refractoriness to previous tranquilizing drugs N = 805 (completers 692) Age: mean age 36 years, ranging up to 51 years Sex: 805 M, 0 F	
Interventions	1. Chlorpromazine, 400mg/day, N = 170 completers 2. Promazine, 400mg/day, N=171 completers 3. Phenobarbital, 200mg/day, N=173 completers 4. Placebo, N = 178 completers “Initiation of medication was gradual, beginning with 1 capsule on the first day of the study, 2 on the second, 3 on the third and full dose of 4 capsules daily thereafter. All medication were given orally, divided into 2 or 3 daily doses given at least eight hours apart.”	
Outcomes	1. Overall efficacy (MSRPP) 2. Dropouts due to any cause, inefficacy, side effects Not usable: Clinical Estimate of Psychiatric Status (CEPS), Taylors Manifest Anxiety Scale (MAS), adverse events	
Notes	'Chlorpromazine was more effective in reducing morbidity than promazine, phenobarbital, or placebo. Promazine was superior to each of the two control medications. The latter two did not differ from each other.'	
Risk of bias		
Bias	Judgment	Support for judgment
Random sequence generation (selection bias)	Unclear	‘Patients selected within each of the four categories of chronicity and disturbance were randomly distributed among four treatment groups‘, 'Patients nominated for the study were assigned medication in random order', no further details
Allocation concealment (selection bias)	Unclear	'Each patient's supply of medication was labeled only with his name and the code number’; 'the list of 800 patients will be randomized in the Central Unit.', no further details
Blinding of participants and personnel (performance bias)	Low	‘Double-blind, 'odorless and identical capsules in appearance and taste', 'Neither the patients nor their physicians knew which of the

		four agents was assigned. As a safeguard, the manager of the hospital was provided with this information for release only if the welfare of the patients so dictated. As pharmacologic and side-effects might impair "double-blind" conditions, using two tranquilizers reduced the chances of identifying the drugs'
Blinding of outcome assessment (detection bias)	Low	As above
Incomplete outcome data (attrition bias)	Unclear	Per-protocol analysis. Attrition ratio (14%), reasons for dropouts not explicitly reported for each arm, but 'The number of patients dropped during the course of the study because of serious side-reactions, inadequate evaluation, or other reasons was distributed evenly among the categories.'
Selective reporting (reporting bias)	Unclear	Mean values of total MSRPP presented on figures, but no raw data on subscales of MSRPP, CEPS and MAS. Narrative description of only significant results.
Other bias	Low	ANCOVA to adjust for baseline values and multiple comparison tests to reduce false positive
Notes on data extraction		
• Sample size of each arm: total participants divided by the number of arms (randomization, evenly distributed, large number of total sample size) • 'Any' response: imputation from baseline and endpoint values of MSRPP and standard deviation for each drug with a threshold of 20% • 'Good' response: same as above using a threshold of 50% • Overall symptoms: total morbidity score of MSRPP, standard deviation from reported alpha level 0.05 • Positive symptoms: narrative description of significant results • Negative symptoms: narrative description of significant results • Dropouts due to any cause: subtraction of the number completers from number after randomization • Dropouts due to inefficacy: of the 18 dropouts due to inefficacy ('increased disturbance'), 10 patients were on antipsychotic treatment. It was assumed that the patients were equally divided among the antipsychotic (5 each) and placebo arms (4 each). • Dropouts due to side effects: Seven patients on antipsychotics were discontinued prematurely due to side effects as well as one on phenobarbital. It was assumed that equal number of patients on each antipsychotic discontinued due to side effects		

B. Casey 1960b

Study characteristics	
References	(Bennett and Kooi, 1961; Casey *et al.*, 1960b; Marks, 1963)
Methods	Allocation: randomized; no further details Blindness: double-blind Design: parallel Duration: 12 weeks; shorter-term Washout duration: unclear; not mentioned Dosing schedule: flexible, oral Location: Veteran Administration Hospitals, USA Setting: 35 centers, inpatients

	Funding: unclear; Squib Sonn, Smith, Klein & French Laboratories, Warner-Chilcott Laboratories, Scherin Corproration (donation of drugs)	
Participants	Diagnosis: newly admitted male patients with schizophrenia History: 7.25 years since first time of treatment, 59% more than one hospitalization; 66% used tranquilizers before, no further information N= 640 (completers 472) Age: mean age 34 years, ranging from 18-54 years Sex: 640 M, 0 F	
Interventions	1. Chlorpromazine, mean dose 635 mg/day, ranging from 200-1200 mg/day, N= 77 completers 2. Trifluprомazine, mean dose 175 mg/day, ranging from 50-300 mg/day, N= 69 completers 3. Mepazine, mean dose 190 mg/day, ranging from 50-300 mg/day, N=? 4. Prochlorperazine, mean dose 90 mg/day, ranging from 25-150 mg/day, N= 83 completers 5. Perphenazine, mean dose 50 mg/day, ranging from 16-96 mg/day, N= 77 completers 6. Phenobarbital, mean dose 120 mg/day, ranging from 32-192 mg/day, N=?	
Outcomes	1. Overall efficacy (MSRPP) 2. Dropouts due to any cause, inefficacy and adverse events Not usable: CEPS, adverse events	
Notes	All phenothiazines were superior to phenobarbital in all instances. Mepazine less effective at the doses employed than the other 4 phenothiazines.	
Risk of bias		
Bias	Judgment	Support for judgment
Random sequence generation (selection bias)	Unclear	'random assignment', no further details
Allocation concealment (selection bias)	Unclear	'identical appearing capsules were supplied to the hospitals from a central point', no further details
Blinding of participants and personnel (performance bias)	Low	‘double-blind’, 'identical appearing capsules'
Blinding of outcome assessment (detection bias)	Unclear	As above
Incomplete outcome data (attrition bias)	High	Type of analyses unclear (per protocol possibly done). High attrition (26.25%), not reasons for dropouts for each arm are clearly described.
Selective reporting (reporting bias)	Unclear	Mean values presented for total morbidity scores, statistical appendix with details, no data available for positive, negative symptoms, CEPS
Other bias	Low	ANCOVA to adjust for baseline measures and correction with multiple range tests
Notes on data extraction		
• Sample size of each arm: total participants divided by the number of arms (randomization, evenly distributed, large number of total sample size) • ‘Any’ response: imputation from baseline and endpoint value of MSRPP and standard deviation for each drug with a threshold of 20% • ‘Good’ response: same as above using a threshold of 50% • Overall symptoms: total morbidity score of MSRPP, standard deviation calculated from F-values between antipsychotic arms and phenobarbital arms • Positive symptoms: narrative description • Negative symptoms: narrative description • Dropouts due to any cause: reported		

- Dropouts due to inefficacy: reported
- Dropouts due to side effects: reported

C. Clark 1961

Study characteristics		
References	(Clark *et al.*, 1961; Clark *et al.*, 1963; Ray *et al.*, 1964)	
Methods	Allocation: randomized; no further details Blindness: double blind Design: parallel Duration: 16 weeks; longer-term Washout period: 13 months preliminary observation with discontinuation of all therapies, followed by 8 weeks placebo administration Dosing schedule: flexible, oral Location: Central State Griffin Memorial Hospital, Norman, Oklahoma, USA Setting: single center, inpatients Funding: NIMH; Smith, Klein & French Laboratories (generously supplied the drugs of the study)	
Participants	Diagnosis: chronic schizophrenic women (DSM-I) History: mean 13 years of continuous hospitalization ranging from 3-24 years, 45 patients (75%) had used previously 'psychoactive drugs', no further information N= 60 Age: mean 43 years, ranging from 26-52 years (data from 57 completers) Sex: 0 M, 60 F	
Interventions	1. Chlorpromazine, mean 691mg/day, 375-800 mg/day, N=20 2. Phenobarbital, mean 388 mg/day, 120-480 mg/day, N=20 3. Placebo, N=20 After gradual increase of the dose “medication was given in 2 capsules, 4 times daily unless individual adjustments were made”	
Outcomes	1. Response to treatment 2. Dropouts due to any cause, inefficacy, side effects Not usable: Oklahoma Behavioral Scale rated by ward personnel and a study-defined scale rated by psychologist, psychological tests, adverse events	
Notes	'While significant chlorpromazine effects were found in all major areas of evaluation, it failed to produce significant effects on time estimation, the Drawing Completion Test, and the withdrawn or underactive aspects of behavior measured by the behavior scale and the psychologists' scaled ratings. No significant effects of phenobarbital were found'	
Risk of bias		
Bias	Judgment	Support for judgment
Random sequence generation (selection bias)	Unclear	'The 60 subjects were rated on the Oklahoma Behavior Scale and, on the basis of these scores, were individually matched into triplets. Random assignment of triplet members to treatment groups resulted in 3 matched groups of 20', no further details
Allocation concealment (selection bias)	Unclear	No further details
Blinding of participants and personnel (performance bias)	Low	'Double blind', 'neither the patients nor the personnel involved in the care or evaluation of the subjects were informed of any individual's medication until the end of the study. Medications were dispensed

		in individually labeled bottles so that identification by code was not possible', 'Identical appearing capsules'
Blinding of outcome assessment (detection bias)	Low	As above
Incomplete outcome data (attrition bias)	Unclear	Per protocol analysis, with low attrition rate (3/60, one of each group) 'removal of a triplet when one of its members developed agranulocytosis in 12th week of chlopromazine treatment'
Selective reporting (reporting bias)	Unclear	The primary outcomes are presented, but not all of the secondary outcomes are presented
Other bias	Unclear	Rescue medication use of fast-acting barbiturates in unmanageable behavior
Notes on data extraction		
• Sample size of each arm: reported • 'Any' response: 'clearly exhibited clinical significant improvement' • 'Good' response: 'clearly exhibited clinical significant improvement' • Overall symptoms: not used, study defined and or not appropriate scales, e.g. ward behavior scale rather than scale of schizophrenia symptoms (Oklahoma Behavioral Scale, study-defined psychologist scale) • Positive symptoms: same as above • Negative symptoms: same as above • Dropouts due to any cause: reported • Dropouts due to inefficacy: reported • Dropouts due to side effects: reported		

D. Gallant 1965

Study characteristics	
References	(Gallant *et al.*, 1965; Gallant *et al.*, 1964)
Methods	Allocation: randomized; no further details Blindness: double-blind Design: parallel Duration: 10 weeks; shorter-term Washout period: patients received no medication for at least 2 months Dosing schedule: flexible, oral Location: Tulane Drug Research Ward of East Louisiana State Hospital, Jackson, Louisiana Setting: single center, inpatients Funding: NIMH; Mc Neil Laboratories (supplied the drugs)
Participants	Diagnosis: chronic patients with schizophrenia History: duration of hospitalization ranged from 3-27 years; no further details on previous medications N= 60 Age: ranging from 21-59 years Sex: 30 M, 30 F
Interventions	1. Trifluperidol, 4-6 mg/day, N=20 2. Trifluoperazine, 32-48 mg/day, N=20 3. Phenobarbital, 120-180mg/day, N=20 *Flexible dosing: maximum dose, unless the occurrence of extrapyramidal symptoms, then switched and maintained with minimum dose (15/20 patients on trifluperidol and 8/20 on trifluoperazine)
Outcomes	1. Response to treatment Not usable: Tulane test battery, no mean values on PRP, Beckomerga rating scale, adverse events, symptoms after withdrawal of the drugs.

Notes	The authors concluded that trifluperidol and trifluoperazine are qualitatively similar in therapeutic action and both superior to phenobarbital	
Risk of bias		
Bias	Judgment	Support for judgment
Random sequence generation (selection bias)	Unclear	'This study included 60 male and female chronic schizophrenics divided at random into 3 groups, equated on the variables of sex, age and length of hospitalization.', no further details
Allocation concealment (selection bias)	Unclear	No further details
Blinding of participants and personnel (performance bias)	Low	'Each of the drugs was supplied in capsules of identical appearance (Parke-Davis 2 pink) and were dispensed in individual medication bottles. This procedure not only insures that all personnel involved in the project remain "blind" as to the medication each patient receives, but also prevents the nursing personnel from learning which patients are receiving the same drug'.
Blinding of outcome assessment (detection bias)	Low	As above
Incomplete outcome data (attrition bias)	Unclear	Responder rates are reported for the whole data set. No mention of dropouts, type of analysis of continuous outcomes.
Selective reporting (reporting bias)	High	Only p-values and not mean values for PRP, Beckomerga rating scale, Tulane test battery
Other bias	Unclear	-
Notes on data extraction		
• Sample size of each arm: reported • 'Any' response: slightly improvement + moderately improved + markedly improved • 'Good' response: moderately improved + markedly improved • Overall symptoms: not reported mean values of Beckomerga Rating Scale, PRP, Tulane Test Battery, only p-values • Positive symptoms: not reported mean values, only p-values • Negative symptoms: not reported mean values, only p-values • Dropouts due to any cause: not reported • Dropouts due to inefficacy: not reported • Dropouts due to side effects: not reported		

E. Holden 1968

Study characteristics	
References	(Holden and Itil, 1969; Holden and Holden, 1970; Holden *et al.*, 1968)
Methods	Allocation: randomized; no further details Blindness: double-blind Design: crossover Duration: 8 weeks of the first crossover phase; shorter-term Washout period: 8 weeks of placebo washout Dosing schedule: fixed (in mg/kg), oral Location: Department of Psychiatry, Missouri Institute of Psychiatry, University of Missouri School of Medicine, St Louis, USA Setting: single center, inpatients

	Funding: NIMH and La Roche, Sandoz Pharmaceuticals	
Participants	Diagnosis: patients with chronic schizophrenia (7 hebephrenic, 6 paranoid, 1 catatonic, 8 undifferentiated, 2 not indicated) History: mean years of current hospitalization 4.1 ranging from 1-10 years, mean duration of illness 8 years, ranging from 5-16 years; previously on treatment, not sufficiently improvement with previous medications N= 24 Age: mean 33 years, ranging from 19-44 years Sex: 24 M, 0 F	
Interventions	1.Thioridazine 300-500 mg/day, N = 8 2. Chlordiazepoxide 60-100 mg/day, N = 8 [3. Thioridazine 150-250 mg/day + Chlordiazepoxide 30-50 mg/day, N =8]	
Outcomes	1. Dropouts due to any cause, inefficacy and side effects Not usable outcomes: responder, CGI-S, BPRS, Itil-Keskiner Rating scale, adverse events (reported for the whole crossover phases, or insufficiently reported)	
Notes	Using aggregated data of the study the authors concluded that thioridazine and combination of thioridazine with chlordiazepoxide at half strength each were effective in 22/22 patients who completed the study, while chlordiazepoxide 11/22.	
Risk of bias		
Bias	Judgment	Support for judgment
Random sequence generation (selection bias)	Unclear	'The patients were randomly divided into three groups, each group following a different medication sequence'
Allocation concealment (selection bias)	Unclear	No further details
Blinding of participants and personnel (performance bias)	Low	'double-blind', 'identical capsules'
Blinding of outcome assessment (detection bias)	Low	'The study was structured on a double blind crossover basis, with a physician from another ward arranging changes in medication.', possibly done
Incomplete outcome data (attrition bias)	Unclear	Per protocol analysis. Low attrition ratio (2/24) and reasons and number of dropouts are presented
Selective reporting (reporting bias)	High	No results of the first crossover phase are presented (apart from dropouts), no raw data on the rating scales
Other bias	Unclear	-
Notes on data extraction		
• Sample size of each arm: reported • 'Any' response: not reported • 'Good' response: not reported • Overall symptoms: no mean values reported for BPRS or the other scales • Positive symptoms: as above • Negative symptoms: as above • Dropouts due to any cause: reported • Dropouts due to inefficacy: reported • Dropouts due to side effects: reported		

F. Hollister 1960

Study characteristics

eAppendix 4. Characteristics of included and excluded studies

References	(Hollister *et al.*, 1960)	
Methods	Allocation: randomized; no further details Blindness: double blind Design: parallel study Duration: 16 weeks; longer-term Washout period: none Dosing schedule: fixed doses based on previous chlorpromazine treatment (‘After entering the blind study each patient was assigned a set of medication from which his daily dosage was one capsule for each 100 mg. of his previous chlorpromazine dose’), oral Location: Veterans Administration Hospital, Palo Alto, California, USA Setting: single center, inpatients Funding: unclear; Smith, Kline & French laboratories (generously supplied trifluoperazine)	
Participants	Diagnosis: male patients with chronic schizophrenic reactions continuously hospitalized for at least 2 years History: chronic, median duration of illness 7 years; continuous current hospitalization with a median of 2 years; treated with chlorpromazine for at least six months, no report if the patients were stable but the general chronic patients were described as: ‘Because of the epochs of war determining admission to veterans hospitals, those psychiatric patients still hospitalized arc an increasingly chronic group that has already been refractory to previous psychotherapeutic, rehabilitative, or somatic treatments’ N = 60 Age: median 36 years, only 5 patients were more than 50 years old Sex: 60 M, 0 F	
Interventions	1. Chlorpromazine, median 300mg/day, ranging from 100-900 mg/d, N = 20 2. Trifluoperazine, median 15 mg/day, ranging from 5-45 mg/d, N = 20 3. Phenobarbital, median 96 mg/day, ranging from 32-288 mg/d, N = 20 “No more than two capsules were administered simultaneously, the frequency of administration being determined by the total daily dosage. The number of capsules given varied from one to nine daily, with a median dosage of three.”	
Outcomes	1. Response to treatment Not usable outcomes: no dropout was mentioned, Hospital Adjustment Scale, adverse events, relapse	
Notes	Both trifluoperazine and chlorpromazine were superior to phenobarbital. Neither of the two phenothiazines was clearly superior over the other.	
Risk of bias		
Bias	Judgment	Support for judgment
Random sequence generation (selection bias)	Unclear	'assignment of medication sets was made random', no further details
Allocation concealment (selection bias)	Unclear	No further details
Blinding of participants and personnel (performance bias)	Low	'double-blind', 'each of the three drugs was put in capsules and packaged so they could not be identified, only code numbers appearing on the labels'
Blinding of outcome assessment (detection bias)	Unclear	As above, no further details
Incomplete outcome data (attrition bias)	Unclear	Responder rates are presented for the whole dataset. No dropout was mentioned, or the type of analysis.
Selective reporting (reporting bias)	High	Scales of improvement are not reported, neither the raw data of Hospital Adjustment Scale

Other bias	Unclear	All patients were previously on treatment with chlorpromazine for at least six months.
Notes on data extraction		
• Sample size of each arm: reported • 'Any' response: improvement (slight + moderate + marked) • 'Good' response: not reported separately • Overall symptoms: not reported • Positive symptoms: not reported • Negative symptoms: not reported • Dropouts due to any cause: dropouts not reported • Dropouts due to inefficacy: dropouts not reported • Dropouts due to side effects: dropouts not reported		

G. Kurland 1960

Study characteristics	
References	(Kurland *et al.*, 1961a; Kurland *et al.*, 1961b; Kurland *et al.*, 1962; Kurland and Sutherland, 1960)
Methods	Allocation: randomized; no further details Blindness: double-blind Design: parallel Duration: 6 weeks; shorter-term Washout period: 48 hours drug-free period Dosing schedule: flexible, oral (i.m. administration the first two days) Location: Spring Grove State Hospital, Baltimore, Maryland, USA Setting: single center, inpatients Funding: NIMH; Smith, Klein & French Laboratories, ER Squib and Sons, Warner-Chilcott Laboratories ('encouragement and support')
Participants	Diagnosis: newly admitted patients, candidates for tranquilizing drugs, i.e. anxiety, agitation and restlessness: predominately schizophrenic in character, excluding patients with concomitant alcohol use disorder, court orders, chronic brain syndrome, major organic disease and senile History: no further information N= 277 Age: mean 39 years, ranging from 18 to 61 years Sex: male to female 1:2 ratio
Interventions	1. Promazine, mean dose 438.92 mg/day, ranging from 300-1600 mg/d, N = 32 2. Chlorpromazine, mean dose 401.35 mg/day, ranging from 300-1200 mg/d, N = 33 3. Mepazine, mean dose 135.45 mg/day, ranging from 75-450 mg/d, N = 34 4. Triflupromazine, mean dose 110.46 mg/day, ranging from 75-300 mg/d, N = 36 4. Prochlorperazine, mean dose 45.38 mg/day, ranging from 30-125 mg/d, N = 32 5. Perphenazine, mean dose 30.83 mg/day, ranging from 24-96 mg/d, N = 36 6. Phenobarbital, mean dose 183.64 mg/day, ranging from 97.5-360 mg/d, N = 37 7. Placebo, N = 37
Outcomes	1. Overall efficacy (MSRPP) 2. Positive symptom (1st order factors of MSRPP: perceptual and conceptual disorganization, 2nd order factor of MSRPP: paranoid belligerence) 2. Dropouts due to any cause, inefficacy and side effects Not usable: PRP, Psychiatric Scale of Target Symptoms (insufficiently reported), adverse events

Notes	'In summary, the drugs studied tended to fall into two groups in the extent to which they reduced MSRPP total morbidity: perphenazine, prochlorperazine, triflupromazine and chlorpromazine were therapeutically more effective than mepazine, promazine, phenobarbital and the placebo'	
Risk of bias		
Bias	Judgment	Support for judgment
Random sequence generation (selection bias)	Unclear	'… acutely disturbed patients were selected for phenothiazine therapy on the basis of target symptoms. They were then randomly assigned to a six-week treatment course with one of the following…'
Allocation concealment (selection bias)	Unclear	'As each newly admitted patient was assigned to a ward physician, the latter was required to make a decision as to whether the patient was to be placed on a tranquilizing drug. The criterion was the presence of target symptoms (anxiety, agitation, hostility), as decided in orientation conferences between doctors and research personnel. If the psychiatrist's decision was in the affirmative, he was required to notify the Research Department and to allow 48hours to elapse so that the Department might obtain necessary evaluations and assign medication', 'This information was secured from the pharmacist', no further information
Blinding of participants and personnel (performance bias)	Low	'double blind', 'identical color', 'all clinical and research personnel working with the patients were bound to the double-blind stipulation imposed by the research plan'
Blinding of outcome assessment (detection bias)	Low	As above
Incomplete outcome data (attrition bias)	High	Analysis with 68% of the sample staying at least one week in the trial, high attrition ratio (~79%). Reasons for dropouts are reported for each arm
Selective reporting (reporting bias)	Unclear	Mean values are reported only at 2 weeks for some outcomes. For primary outcome, they are reported at both two weeks and endpoint.
Other bias	Unclear	Highly disturbed patients were not referred, possibly physicians were unwilling to leave patients without treatment for 48 hours evaluation period
Notes on data extraction		
• Sample size of each arm: reported • 'Any' response: imputation from baseline and endpoint value of MSRPP and standard deviation for each drug with a threshold of 20%		

- ‘Good’ response: same as above using a threshold of 50%
- Overall symptoms: reported mean values for total morbidity score of MSRPP, standard deviations extracted from reported alpha 0.05 between antipsychotic drugs and phenobarbital, average standard deviation for non-significant differences, i.e. mepazine and promazine versus phenobarbital
- Positive symptoms: first order ‘conceptual disorganization’ and ‘perceptual disorganization’ and second order ‘paranoid belligerence’ of MSRPP, as above extracted the standard deviation. Logarithmic transformed values for perceptual disorganization and paranoid belligerence were extracted.
- Negative symptoms: not reported at endpoint
- Dropouts due to any cause: reported
- Dropouts due to inefficacy: reported
- Dropouts due to side effects: reported

H. Merlis 1962

Study characteristics		
References	(Merlis *et al.*, 1962)	
Methods	Allocation: randomized; no further details Blindness: double-blinded Design: parallel Duration: 4 weeks; shorter-term Washout period: 2 weeks withdrawal of previous treatment Dosing schedule: flexible, oral (‘'Flexible doses were suggested, but all patients were given fixed doses in fear of side effects (apart from one patient on chlorpromazine with medication doubled, one on diazepam with dose reduced to 10mg due to vomiting, and three on chlordiazepoxide with reducing only for one week to 25mg ') Location: Central Islip State Hospital, Central Islip, N.Y Setting: single center, inpatients Funding: NIMH and Roche	
Participants	Diagnosis: chronic psychotic patients: 70/80 schizophrenia (32 paranoid 12 hebephrenic, 12 catatonic, 14 not specified), 5 patients with psychopathic personality and 5 with mental deficiency History: chronic patients with about 57/80, 2 or more years length of hospitalization, 66/80 first admissions; all had received a variety of psychopharmacological agents (phenothiazines most frequently) N= 80 Age: range 14-62 years (only 3 under 20) Sex: 40 M, 40 F	
Interventions	1. Chlorpromazine 150 mg/day, N = 20 2. Chlordiazepoxide 75 mg/day, N = 20 3. Diazepam 30 mg/day, N = 20 4. Placebo, N = 20	
Outcomes	1. Response to treatment (response based on BPRS and MMS, without referring to any cut-off)	
Notes	No difference among drugs or placebo	
Risk of bias		
Bias	Judgment	Support for judgment
Random sequence generation (selection bias)	Unclear	‘the patients randomly selected would receive medication’, no further details
Allocation concealment (selection bias)	Unclear	No further details
Blinding of participants and personnel (performance bias)	Low	'double blinded study', 'capsules of identical appearance identified by the ward only by code letter'
Blinding of outcome assessment (detection bias)	Unclear	As above, no further detail
Incomplete outcome data (attrition bias)	Unclear	Whole data set for response. No mention on dropouts and type of analysis

Selective reporting (reporting bias)	High	Narrative results of description, no mean values for BPRS, Malamud Sand Scale
Other bias	Unclear	Inexperienced raters of BPRS
Notes on data extraction		
• Sample size of each arm: reported • 'Any' response: average of responders based on BPRS and MMS, no criteria for response described • 'Good' response: insufficiently reported • Overall symptoms: no mean values of BPRS or Malamud Sand Scale • Positive symptoms: not reported • Negative symptoms: not reported • Dropouts due to any cause: not reported • Dropouts due to inefficacy: not reported • Dropouts due to side effects: not reported		

I. Vestre 1962

Study characteristics		
References	(Vestre, 1965; Vestre *et al.*, 1962)	
Methods	Allocation: randomized; no further details Blindness: double-blinded Design: parallel Follow up duration: 12 weeks; shorter-term Washout period: 2 weeks placebo washout (not specified if inert; possibly phenobarbital) Dosing schedule: flexible, oral Location: Veterans Administration Hospital, St Cloud, Minn, USA Setting: single center, inpatients Funding: NIMH; Squibb Institute for Medical Research (supplied with courtesy the drugs of the study)	
Participants	Diagnosis: male patients with schizophrenia from the intensive treatment ward History: 60% first time hospitalization; 4 1/3 years of hospitalization ranging from 3 months-17 years; 'all had been undergoing ataractic medication' 'these therapies apparently had been of some benefit, but most of the patients continued to require supervision and close-ward care' N= 93 Age: mean 37 years, ranging from 25-56 years Sex: 93 M, 0 F	
Interventions	1. Fluphenazine, mean dose 10mg/day, ranging from 2.5-25 mg/day, N = 31 2. Trifluprомazine, mean dose 130mg/day, ranging from 25-250 mg/day, N =31 3. Phenobarbital, mean dose 130mg/day, ranging from 32-320 mg/day, N =31	
Outcomes	1. Response to treatment ('any', 'good') 2. Overall efficacy (total PRP) 3. Positive symptoms (PRP thinking disorganization) 4. Dropout due to any cause, inefficacy and side effects Not usable: other PRP subscales, MMPI, adverse events	
Notes	The two phenothiazines were more effective than phenobarbital	
Risk of bias		
Bias	Judgment	Support for judgment
Random sequence generation (selection bias)	Unclear	'randomly assigned to three groups', no further details
Allocation concealment (selection bias)	Unclear	No further details

Blinding of participants and personnel (performance bias)	Low	'double blinded study', 'identical capsules'
Blinding of outcome assessment (detection bias)	Low	'Since the double blind code was not broken until after the final evaluations had been completed, the ward physician did not, at this point, know the identity of the test medication'
Incomplete outcome data (attrition bias)	Unclear	Whole data set for response to treatment, type of analyses for continuous outcomes unclear (possible per protocol analysis). Reasons and number of dropouts are mentioned for each drugs, attrition ratio (~12%).
Selective reporting (reporting bias)	Unclear	Missing standard deviation or statistics for subscales of PRP (paranoid belligerence, e.g. withdrawal)
Other bias	Low	ANCOVA to adjust for baseline scores
Notes on data extraction		
• Sample size of each arm: reported • 'Any' response: slightly improvement + moderately improvement + markedly improvement • 'Good' response: moderately improvement + markedly improvement • Overall symptoms: total score of PRP, extracted from p values (reported alpha 0.05 and 0.2) • Positive symptoms: 'thinking disorder' of PRP, standard deviation extracted from reported alpha 0.05, but only mean values of 'paranoid belligerence' of PRP (standard deviation not extractable) • Negative symptoms: reported mean values, standard deviations not extractable • Dropouts due to any cause: reported • Dropouts due to inefficacy: reported • Dropouts due to side effects: reported		

2. Records that were counted as duplicates

A. Bennet 1961

Bennet 1961(Bennett and Kooi, 1961) was counted as a part of the multicenter study of the Veteran Administration Hospitals Casey 1960b (Casey *et al.*, 1960b). The hospital and the authors of Bennet 1961 were mentioned as contributors in Casey 1960b, while these studies had similar inclusion criteria, drugs and dose schedule, treatment duration as well as outcomes. However, there were no other available information in order to clarify that Bennet 1961 was part of the Casey 1960b. Bennet 1961 found that antipsychotic drugs were more effective than phenobarbital, with 14/25 of the patients on phenothiazines had a clinical response (12 clinical remission, two much improved, 4 improved, 7 unimproved), while none of the patients on phenobarbital improved (0 out of 5). We employed the conservative approach by treating Bennet 1961 as part of the Casey 1960b, in order to avoid counting twice part of the same population.

B. Gallant 1965

Gallant 1964 (Gallant *et al.*, 1964) reported the acute withdrawal of the treatment after a double blind study, which had the same authors, funding, participants, drugs and doses, follow-up period with Gallant 1965 (Gallant *et al.*, 1965).

C. Vestre 1965

Vestre 1965 (Vestre, 1965) and Vestre 1962 (Vestre *et al.*, 1962) had similar number of participants, drugs and doses, follow up period as well as the same funding. Vestre 1965 was a brief report with ten less participants, which might have been assessed with additional psychological tests. It was treated as part of Vestre 1961, without any other available information. It did not provide any relevant to the review data.

3. Description of the rating scales with useable data

Data from the currently used PANSS or the BPRS were not available in these old studies. Two previously published scales for schizophrenia were used in the data extraction: the Lorr's Multidimensional Scale of Rating Psychiatric Patients (MSRPP) (Lorr *et al.*, 1953) in three studies (Casey *et al.*, 1960a; Casey *et al.*, 1960b; Kurland *et al.*, 1961a), and the Psychotic Reaction Profile (PRP) (Lorr *et al.*, 1960) in another study (Vestre *et al.*, 1962). The MSRPP has 62 items, 40 rated by psychiatrists or psychologists and 22 by ward personnel, with 3 to 4 points each, starting from one. Higher scores means higher severity. The total morbidity score of MSRPP were also used for the imputation of the number of responders in three studies (Casey *et al.*, 1960a; Casey *et al.*, 1960b; Kurland *et al.*, 1961a), according to the methodology described by Samara MT, et al 2013 (Samara *et al.*, 2013). The PRP is an 85-item scale adaption of the MSRPP by Lorr and was rated only by ward personnel. Other scales were insufficiently reported, e.g. BPRS (Merlis *et al.*, 1962), or not appropriate, such as study defined scales and or scales of ward behavior rather than schizophrenia symptoms, e.g. Oklahoma Behavioral Scale (Clark *et al.*, 1961) and a modified version Behavioral Disturbance Index (Cohler *et al.*, 1966).

Overall symptoms were derived by the total morbidity scores of MSRP and PRP. MSRPP and PRP have four subscales, i.e. thinking disorder, paranoid belligerence, withdrawal and agitated depression. Regarding positive symptoms, 'thinking disorder' and 'paranoid belligerence' were extracted separately. The second order subscales of MSRPP are constructed from first order subscales. In one study Kurland 1961 (Kurland *et al.*, 1961a), the second order subscale 'thinking disorder' was not available at the endpoint, and the first order subscales 'conceptual disorganization' and 'perceptual disorganization', which contribute to the second order 'thinking disorder', were extracted. The subscale 'withdrawal' was relevant to negative symptoms, though data were not extractable for the meta-analysis.

4. Decisions and estimations on data extraction

The studies were very old and poorly reported, hence conservative decisions and estimates were necessary in order to conduct the meta-analysis.

Meta-analytic decisions:

1. The ITT approach was followed, and when only completer analysis was presented, we conservatively assumed that participants who were lost to follow-up would not have responded. Only two out of the six studies reported ITT results for the primary outcome (Gallant *et al.*, 1965; Vestre *et al.*, 1962). A sensitivity analysis by excluding studies with only completer analyses was conducted (eAppendix-5.3A).
2. Response rates were imputed from overall symptoms using a validated method in three studies (Casey *et al.*, 1960a; Casey *et al.*, 1960b; Kurland *et al.*, 1961a). This method provides conservative estimates of the comparison between interventions (Samara *et al.*, 2013). Sensitivity analysis by excluded studies with imputed responders was conducted (eAppendix-5.3A).
3. The above imputation method requires a response threshold (20% and 50% for 'any' and 'good' response respectively), number of participants, baseline and endpoint means as well as the endpoint standard deviation (Samara *et al.*, 2013). Standard deviations were not reported in these studies and therefore they were estimated using reported test statistics, i.e. the p-value (Casey *et al.*, 1960a; Kurland *et al.*, 1961a; Vestre *et al.*, 1962) and F-values (Casey *et al.*, 1960b). However, the studies were poorly reported and only the threshold of statistical significance was usually reported (at 0.05). The exact p-values as well as the standard deviations might have been smaller. These studies were multi-arm and the weighted average of standard deviation were calculated for the control group (phenobarbital). These estimated standard deviations might be an important reason for introducing heterogeneity in both overall symptoms, as well as 'good' and 'any' response (since responder rates were imputed from overall symptoms for the aforementioned studies). Due to these shortcomings, we conducted sensitivity analyses by using different estimates for the standard deviations, i.e. using the smallest estimate within study or using the estimate from exact F-values (see eAppendix-5.3B).

Further estimations on number of randomized participants and dropouts:

4. The number of patients randomized to each arm and the number of patients included in the analysis were not clearly reported in two studies (Casey *et al.*, 1960a; Casey *et al.*, 1960b). The studies were large (805 and 640 sample sizes) with equal ratio of patients per arm. Therefore, we assumed that the patients were evenly distributed among arms and the number of participants randomized to each arm was estimated. The number of patients included in the analysis, when not reported for some arms, it was also estimated by the number of randomized patients and the number of patients that were excluded from the analysis (including dropouts-see below).
5. The distribution of dropouts to different arms were not clearly reported in one study (Casey *et al.*, 1960a), but narrative descriptions were sufficient to provide estimations. In particular, dropouts due to any cause were calculated by subtracting the number completers from randomized number of patients per arm. About dropouts due to inefficacy, it was reported that out of the 18 dropouts due to inefficacy ('increased disturbance'), 10 patients were on antipsychotic treatment. It was assumed that the patients were equally divided among the antipsychotics (5 in chlorpromazine and 5 in promazine) and placebo arms (4 in phenobarbital and 4 in inactive placebo). About dropouts due to side effects, seven patients on antipsychotics were discontinued prematurely due to side effects as well as one on phenobarbital. It was assumed that equal number of patients on each antipsychotic discontinued due to side effects (4 in chlorpromazine and 3 in promazine).

5. Characteristics of excluded studies

n/n	Study	Reasons for exclusion
1.	Abenson 1964 (Abenson and Beattie, 1964)	Allocation: randomized, crossover Participants: male patients with schizophrenia with total or almost complete catatonic mutism Interventions: i.v. methedrine, i.v. sodium amytal, i.m. trifluoperazine, inj. placebo, i.m. trifluoperazine + i.v. methedrine
2.	Azima 1959 (Azima *et al.*, 1959)	Allocation: randomized Participants: chronic male patients with schizophrenia 'absence of overt restitutional symptoms' Interventions: reserpine, phenobarbital Outcomes: not usable data
3.	Baldaçara 2011 (Baldaçara *et al.*, 2011)	Allocation: randomized Participants: 150 patients with agitation (60.6% psychotic disorder, 39.4% bipolar disorder) Interventions: i.m. olanzapine, i.m. ziprasidone, i.m. haloperidol + promethazine, i.m.haloperidol + midazolam, i.m. haloperidol
4.	Bishop 1966 (Bishop and Gallant, 1966)	Allocation: not randomized (review)
5.	Brill 1964 (Brill *et al.*, 1964)	Allocation: randomized Participants: female outpatients with personality disorder, psychoneuroses, psychosomatic disturbances, borderline schizophrenic states (the latter consisted ~9.7% of the sample). Patients with psychosis were excluded.
6.	Costello 1964 (Costello, 1964)	Allocation: randomized Participants: 40 patients with schizophrenia Interventions: D-amphetamine sulphate, sodium seconal, meprobamate, placebo, no treatment
7.	Crosse 1974 (Crosse, 1974)	Allocation: not randomized
8.	Daston 1959 (Daston, 1959)	Allocation: randomized Participants: chronic patients with schizophrenia Interventions: chlorpromazine, promazine, phenobarbital, placebo Outcomes: no separate data for the first crossover phase
9.	D'Errico 1966 (D'Errico *et al.*, 1966)	Allocation: not randomized
10.	Dysken 1979 (Dysken *et al.*, 1979)	Allocation: not randomized
11.	Endo 1967 (Endo, 1967)	Allocation: not randomized
12.	Esmailian 2015 (Esmailian *et al.*, 2015)	Allocation: randomized Participants: patients 'referred to emergency department because of medical diseases, drug poisoning or trauma and need for sedation
13.	Galbrecht 1968 (Galbrecht *et al.*, 1968)	Allocation: randomized Participants: patients with schizophrenia Interventions: chlorpromazine, fluphenazine, thioridazine Outcomes: EEG recording, pre- and post-treatment with pentothal
14.	Gambill 1966 (Gambill and Wilson, 1966)	Allocation: randomized Participants: male schizophrenics Interventions: ECT and placebo, pentothal and prochlorperazine, ECT and prochlorperazine, pentothal and placebo
15.	Garza-Treviño 1989 (Garza-Treviño *et al.*, 1989)	Allocation: randomized (short duration up to 210 minutes) Participants: patients with agitation (unknown diagnosis) Interventions: i.m. haloperidol + phenobarbital, i.m. thiothixene + lorazepam
16.	Geraud 1970 (Geraud and Escande, 1970)	Allocation: not randomized Participants: patients with psychiatric disorder and insomnia (18% patients with schizophrenia)
17.	Grinspoon 1964 (Cohler *et al.*, 1966; Grinspoon *et al.*, 1964)	Allocation: randomized Participants: chronic patients with schizophrenia Interventions: thioridazine, phenobarbital + atropine Outcomes: not usable data (use of scale for ward behavior rather than schizophrenia symptoms, i.e. Behavioral Disturbance Index)

18.	Hosak 1969 (Hosak and Komenda, 1969)	Allocation: not randomized? Participants: patients with schizophrenia Interventions: insulin alone or in combination with other drugs
19.	Huston 1952 (Cohen *et al.*, 1954, 1956; Huston Paul and Senf, 1952; Senf *et al.*, 1955)	Allocation: not randomized
20.	Hwang 2012 (Huang C *et al.*, 2015; Hwang T *et al.*, 2012)	Allocation: randomized Participants: acutely admitted patients with schizophrenia or related disorders and acute agitation Interventions: i.m. haloperidol + lorazepam, i.m. olanzapine
21.	Itil 1967 (Itil *et al.*, 1967)	Allocation: not randomized
22.	Jensen 2016 (Jensen *et al.*, 2016)	Allocation: not randomized
23.	Joergensen 1986 (Joergensen and Fog, 1986)	Allocation: randomized, crossover design (1 week duration of the first phase) Participants: 11 inpatients with schizophrenia Interventions: i.m. FK 33-824 (encephalin analogue), i.m. phenobarbital
24.	Kabanov 1974 (Kabanov I, 1974)	Allocation: not randomized? Participants: patients with agitation Interventions: inj. chlorpromazine and hexenal combination, inj. chlorpromazine
25.	Kammerer 1969 (Kammerer *et al.*, 1969)	Allocation: not randomized? Participants: hospitalized women with psychotic disorder Interventions: mandrax (methaqualone and diphenhydramine), binoctal (amobarbital), placebo
26.	Kellner 1975 (Kellner *et al.*, 1975)	Allocation: randomized Participants: patients with schizophrenia and anxiety on maintenance treatment with antipsychotics Interventions: augmentation of chlordiazepoxide versus placebo
27.	Kitajima 2012 (JPRN-UMIN000004008, 2010; Kitajima *et al.*, 2012)	Allocation: not randomized
28.	Kornetsky 1959 (Kornetsky *et al.*, 1959)	Allocation: randomized, crossover (2 week duration of first crossover phase) Participants: male patients with schizophrenia Interventions: chlopromazine, secobarbital, placebo Outcomes: not usable outcomes (i.e. performance on psychological tests)
29.	Kramer 1975 (Kramer *et al.*, 1975)	Allocation: high risk of bias for randomization sequence generation (block randomization: 'patients were assigned in blocks of six, with two patients being assigned to each of the three groups', 'When the CGI rating showed difference between drug and control at the 95% confidence intervals, the control group was taken out from the block randomizations'). The final number of participants in each arm deviated from the sample if randomized with block randomization.
30.	Latz 1965 (Latz and Kornetsky, 1965)	Allocation: randomized, crossover (2 weeks first crossover phase on the same treatment) Participants: patients with schizophrenia Interventions: chlorpromazine, secobarbital, placebo (administration on testing days, once a week)
31.	Levin 1959 (Levin M, 1959)	Allocation: quasi-randomized (by sequence)
32.	Linn 1984 (Linn, 1984)	Allocation: not randomized
33.	Little 1958 (Little J, 1958)	Allocation: randomized Participants: chronic patients with schizophrenia Interventions: chlorpromazine, amylbarbitone, inert placebo Outcomes: no separate data for the first crossover phase
34.	Loga 1975 (Loga *et al.*, 1975)	Allocation: randomized (3 weeks first crossover phase) Participants: male patients with schizophrenia Interventions: chlorpromazine + orphenadrine, chlorpromazine + phenobarbitone

35.	Loprete 1967 (Loprete F and Palm, 1967)	Allocation: randomized Participants: newly admitted psychiatric patients (no further details) Interventions: Etrafon Forte, Etrafon (amitriptyline + perphenazine), Dormison (methylpentynol), phenobarbital, usual care
36.	Lorr 1961 (Lorr *et al.*, 1961)	Allocation: randomized Participants: male veteran patients, newly accepted for individual psychotherapy (16% psychotic, 57% psychoneurotic, 27% psychophysiologic and personality disorders)
37.	Maculans 1964 (Maculans G, 1964)	Allocation: randomized Participants: hospitalized psychotic patients (36 from 37 patients with schizophrenia) Interventions: chlorpromazine, chloprothexine, diazepam Outcomes: no separate data for the first crossover phase
38.	Miller 1953 (Miller D *et al.*, 1953)	Allocation: randomized Participants: patients with catatonic schizophrenia Interventions: ECT-induced grand mal, pentothal i.v., pentothal i.v. + non-convulsive simulation
39.	Monroe 1965a (Monroe R and Wise S P, 1965)	Allocation: not randomized
40.	Monroe 1965b (Monroe *et al.*, 1965)	Allocation: unclear randomization (Latin square assignment), crossover (no separate data) Participants: 11 out of 15 were patients with schizophrenic reactions (less than 80% schizophrenia)
41.	Monroe 1975 (Monroe R, 1975)	Allocation: not randomized (review)
42.	Morera-Fumero 2010 (Morera-Fumero A and Abreu-Gonzalez, 2010)	Allocation: not randomized
43.	Murphree 1967 (Murphree H *et al.*, 1967)	Allocation: unclear randomization ('matching placebo') Participants: 15 male healthy controls, 11 male patients with schizophrenia Interventions: phenobarbital, placebo and thiopental procedure
44.	NCT01082263 (NCT01082263, 2011)	Allocation: not randomized
45.	NCT02504476 (NCT02504476, 2016)	Allocation: randomized Participants: healthy subjects, patients with schizophrenia or schizoaffective disorder on antipsychotic medication Interventions: AMG-581, midazolam, placebo
46.	NCT03061136 (NCT03061136, 2017)	Allocation: randomized, crossover Participants: patients with schizophrenia, schizophreniform, schizoaffective disorder Interventions: clonazepam, placebo
47.	Panaccio 1972 (Panaccio and Tétreault, 1972)	Allocation: randomized Participants: psychotic patients with insomnia Interventions: flurazepam, secobarbital, placebo
48.	Pfeiffer 1965 (Pfeiffer C *et al.*, 1965)	Allocation: multiple study designs, not randomized and crossover study regarding administration of antipsychotic drugs
49.	Prakash 1984 (Prakash *et al.*, 1984)	Allocation: not randomized
50.	Rappaport 1967 (Rappaport, 1967)	Allocation: randomized Participants: female patients with acute schizophrenic reaction Interventions: i.m. chlorpromazine, i.m. perphenazine, i.m. sodium pentobarbital, i.m. placebo Outcomes: pre- and post-single dose treatment performance on psychological test
51.	Rashkis 1957 (Rashkis Harold and Smarr Erwin, 1957)	Allocation: not randomized (assignment of patients into 16 groups of three patients based on their baseline severity, the whole groups were assigned into 16 drug group) Participants: chronic catatonic patients with schizophrenia Interventions: 16 combinations of reserpine, trihexyphenidyl, methylphenidate, placebo

52.	Rickels 1969 (Rickels and Hesbacher, 1969)	Allocation: not randomized
53.	Rosner 1955 (Rosner *et al.*, 1955)	Allocation: quasi-randomized (order of admission)
54.	Saletu 1972 (Saletu and Itil T, 1972)	Allocation: not randomized
55.	Schwartz 1971(Schwartz *et al.*, 1971)	Allocation: not randomized
56.	Shader 1964 (Shader *et al.*, 1964)	Allocation: randomized, crossover Participants: 20 healthy subjects
57.	Shopsin 1969 (Shopsin *et al.*, 1969)	Allocation: randomized, 48 hours follow-up duration Participants: patients with acute psychotic behavior and agitation Interventions: i.m. haloperidol, i.m. chlorpromazine, i.m. sodium amobarbital
58.	Sirbu 1965 (Sirbu and Argintaru, 1965)	Allocation: not randomized
59.	Smith 1959 (Smith J *et al.*, 1959)	Allocation: implied randomization from double-blind Participants: patients with schizophrenia Interventions: chlopromazine, promazine, mephobarbital, inert placebo Outcomes: no separate data for the first crossover phase
60.	Smith 1961 (Smith, 1961)	Allocation: not randomized ('the 45 patients divided into three matched groups on the bases of age, duration of illness and predominant symptomatology')
61.	Spyker 2014 (Spyker D *et al.*, 2014a, b, 2015)	Allocation: randomized, crossover Participants: healthy volunteers
62.	St Jean 1967 (St Jean *et al.*, 1967)	Allocation: randomized Participants: male patients with chronic schizophrenia Interventions: propericiazine, chlorpromazine added to previous medications
63.	Stonehill 1966 (Stonehill *et al.*, 1966)	Allocation: unclear randomisation ('Latin square') Participants: chronic psychotic patients Interventions: chlordiazepoxide, diazepam, LA XIV, LA XVII (the latter being benzodiazepine derivatives)
64.	Turner 1958 (Turner W *et al.*, 1958)	Allocation: randomized Participants: patients with schizophrenia Interventions: reserpine, raunormine, phenobarbital Outcomes: not usable data
65.	Uhlenhuth 1977 (Uhlenhuth E, 1977)	Allocation: not randomized
66.	Vikhliaev 1971 (Vikhliaev Iu *et al.*, 1971)	Allocation: not randomized? Intervention: chlordiazepoxide, diazepam, nitrazepam, oxazepam
67.	Villeneuve 1972 (Villeneuve *et al.*, 1972)	Allocation: randomized, (48 hours first crossover) Participants: chronic psychiatric patients with insomnia Interventions: capuride, secobarbital, placebo
68.	Wang 2012 (Wang B *et al.*, 2012)	Allocation: not randomized
69.	Watanabe 1974 (Watanabe, 1974)	Allocation: not randomized
70.	Wikler 1965 (Wikler *et al.*, 1965)	Allocation: not randomized
71.	Wolf 2011 (Wolf D *et al.*, 2011)	Allocation: not randomized
72.	Wyant 1990 (Wyant *et al.*, 1990)	Allocation: randomized, follow up duration of 120 minutes Participants: male patients with schizophrenia with acute exacerbation Interventions: i.m. haloperidol, i.m. midazolam, i.m. sodium amytal

6. References

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eAppendix 5. Results

1. Estimation of event rates and number-needed-to-treat

The effect size for dichotomous outcomes (response and dropouts) was the relative risk and its 95% confidence interval. Absolute event rates and number-needed-to-treat to benefit/harm (NNTB/NNTH) were supplementary presented. They were estimated using relative risks (RR) and as assumed control risk (ACR) the weighted average rate of events in the control group (phenobarbital), according to the calculations provided by the Cochrane Handbook (Higgins and Green, 2011).

The calculations used:

- Event rate in the experimental group (antipsychotics) = 100 * RR * ACR
- NNTB/NNTH = absolute value of [1 / (ACR * (1-RR))]; the confidence intervals of the NTTB/NNTH were calculated using the confidence intervals of the RR

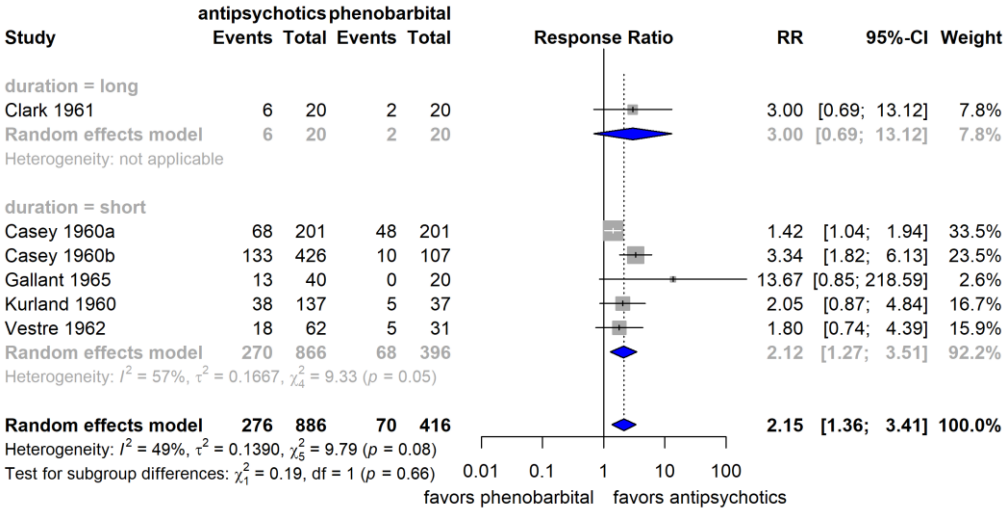
An example using the primary outcome 'good' response (see Results and Figure 3A):

- The response ratios are RR: 2.15 and 95% CI: [1.36-3.41]
- Response rates in the phenobarbital group were ACR = 70 / 416= 0.1683 or 16.83%
- Assumed 'good' response rates in antipsychotics were = RR * ACR = 2.15 * 0.1683 = 0.3618 or 36.18%
- Point estimate of NNTB = absolute value of [(1/ (0.1683 * (1-2.15))] = 5.1 or ~5 by rounding to integer
- Similarly using the 95% of RR the 95% of NNTB are calculated absolute value [(1/ (0.1683 * (1-1.36))] = 16.5 or ~17 and absolute value [(1/ (0.1683 * (1-3.41))] = 2.4 or ~2

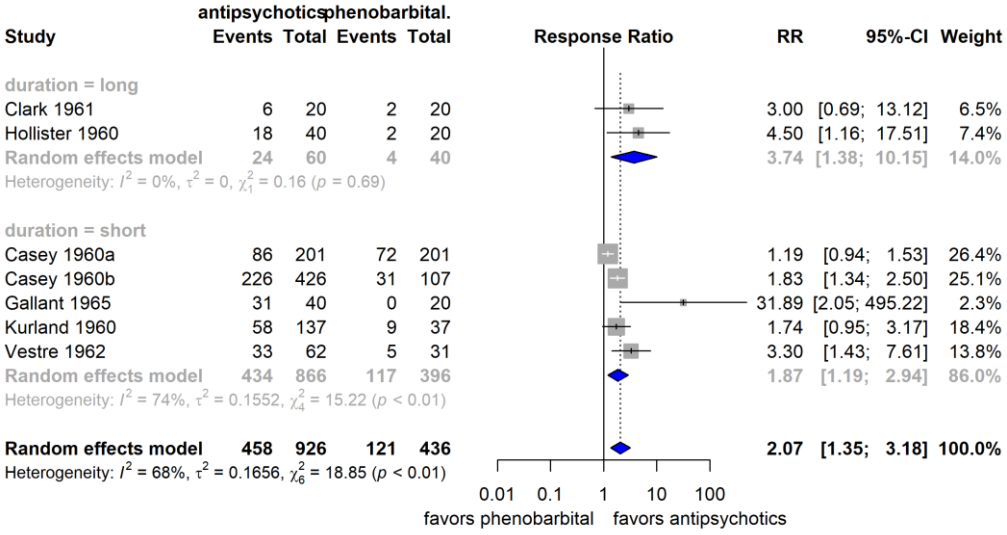
2. Forest plots for shorter- and longer-term results

In contrast to the figures in the main manuscript, in the forest plots below, shorter-term (≤ 3 months) and longer-term results are presented separately. Data for both shorter- and longer-term results were available only for the comparison between antipsychotic drugs and barbiturates. The random-effects model the Mantel-Haenszel method was used in all cases. The weight of each study is reflected by the size of the square and the 95% confidence intervals by the associated error bars. The pooled effect (point estimate and 95% CI) is demonstrated with a blue diamond. Antipsychotic drugs are superior to phenobarbital or benzodiazepines when the response ratio (RR) is greater than one or the relative risk (for premature discontinuation) is lower than one. Heterogeneity across studies is quantified by the I^2 and χ^2 statistics. Events: number of participants who responded or discontinued prematurely, Total: total number of participants in the group.

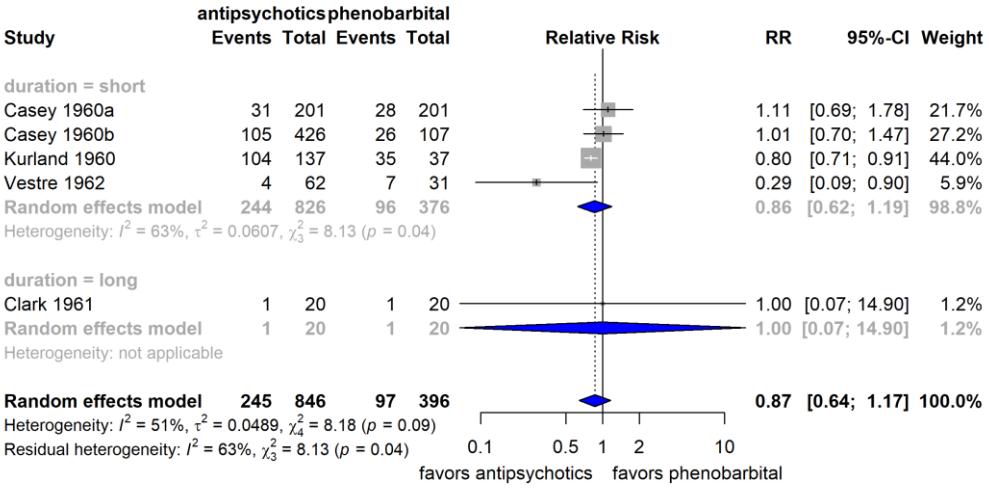
eFigure1. 'Good' response for shorter- and longer-term results.



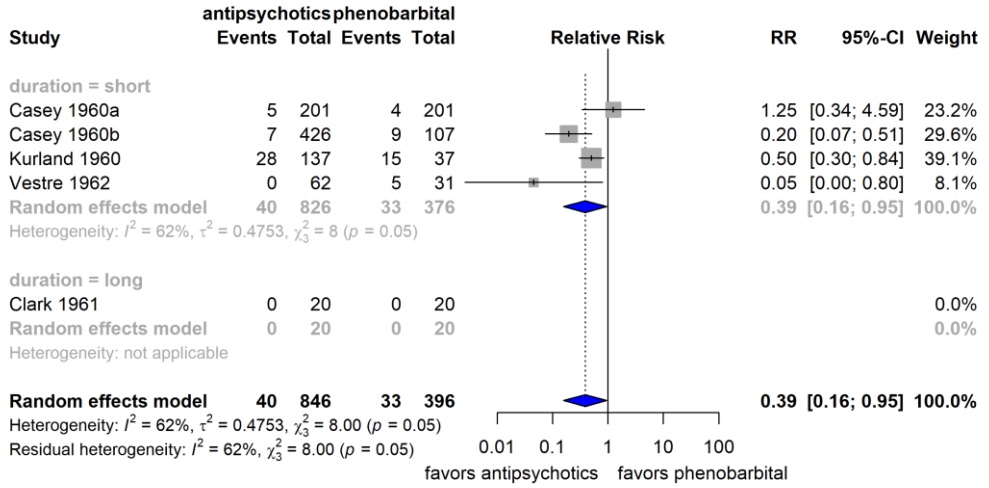
eFigure2. 'Any' response for shorter- and longer-term results.



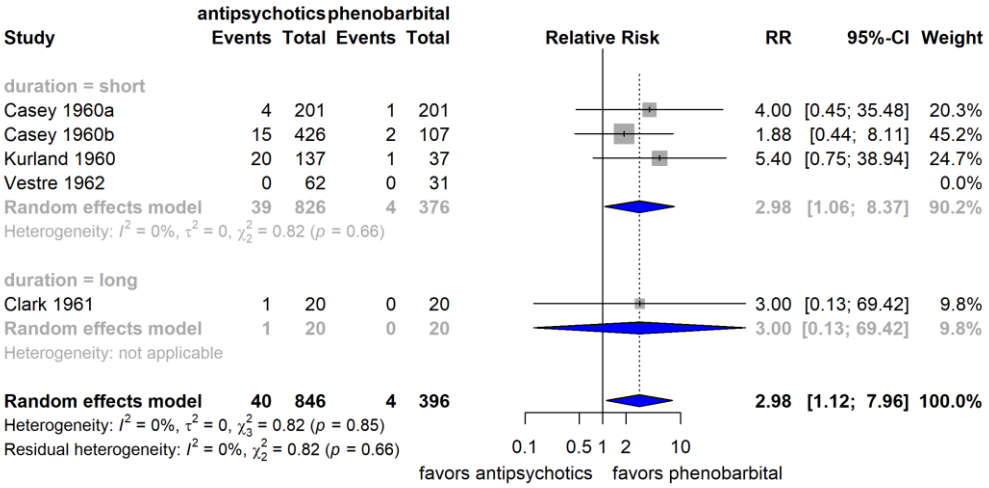
eFigure3. Premature discontinuation due to any cause for shorter- and longer-term results.



eFigure4. Premature discontinuation due to inefficacy for shorter- and longer-term results.



eFigure5. Premature discontinuation due to side effects for shorter- and longer-term results.



3. Sensitivity and post-hoc analyses

A. Sensitivity analyses of the primary outcome.

Sensitivity, subgroup and meta-regression analyses were conducted for the primary outcome ('good' response) regarding the comparison between antipsychotic drugs and barbiturates. Due to the paucity of available data, subgroup, sensitivity and meta-regression analyses were not meaningful for benzodiazepines. A priori defined: fixed effects and exclusion of studies with per-protocol data, Post hoc: inclusion of promazine and mepazine, exclusion of studies with imputed responder rates.

eTable4. Sensitivity analyses of the primary outcome 'good' response.

Effect size (Response Ratio, M-H)					**Heterogeneity**
	N	**Point estimate**	**Lower limit of 95% CI**	**Upper limit of 95% CI**	**I^2 (%)**
Random effects model	6	2.15	1.36	3.41	48.9
Fixed effects model	6	2.03	1.57	2.62	48.9
Including promazine and mepazine	6	1.98	1.07	3.68	71.1
Exclusion of studies with imputed responders (Casey 1960, Casey 1960b, Kurland 1961)	3	2.50	1.07	5.84	13.5
Exclusion of studies with only per-protocol data (Gallant 1965 and Vestre 1962 remain)	2	3.46	0.44	27.05	56.2

N: number of studies, M-H=Maentel-Haenszel, 95% CI=95% Confidence Interval

B. Sensitivity analyses of overall symptoms

Response ratios as well as overall efficacy in our primary analysis may have been underestimated due to conservative decisions and estimates (see eAppendix-4.4). Therefore, we conducted post-hoc sensitivity analyses for overall symptoms by using two scenarios for estimating standard deviations. First, we used the smallest standard deviation estimated within each study. Second, we used the most precise estimate of standard deviation of MSRPP, which was derived from the exact F-values reported (Casey *et al.*, 1960b). In eTable5 and eFigure6-7, the results of the sensitivity analyses are presented. Effect sizes were larger and heterogeneity was smaller (see also eAppendix-5.4 for assessment of heterogeneity based on the empirical distributions of τ^2).

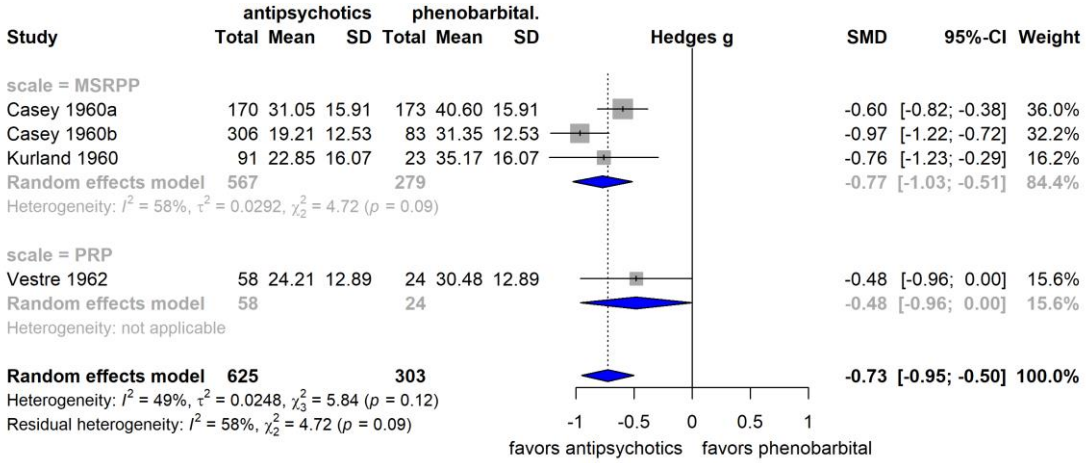
eTable5. Sensitivity analysis using different estimates for standard deviations for overall symptoms

Effect size (standardized mean difference as Hedge's g)				**Heterogeneity**
	Point estimate	**Lower limit of 95% CI**	**Upper limit of 95% CI**	**I^2 (%)**
Primary analysis (Figure 3C)	-0.56	-0.96	-0.16	84
Smallest SD within study (eFigure6)	-0.73	-0.95	-0.50	48.7
MSRPP SD from F-values (eFigure7)	-0.82	-1.01	-0.62	31.6

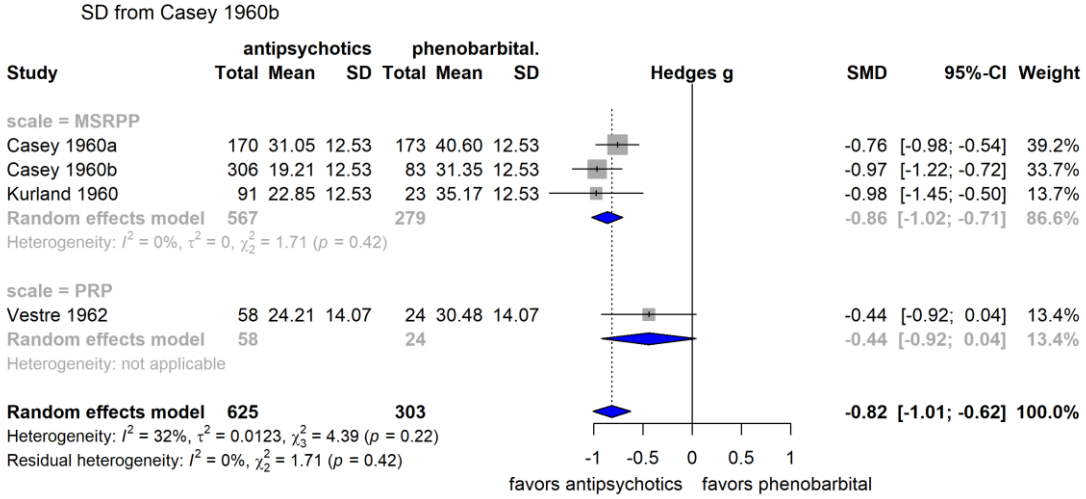
95% CI=95% Confidence Interval

eAppendix 5. Results

eFigure6. Sensitivity analysis using the smallest standard deviation estimated within each study

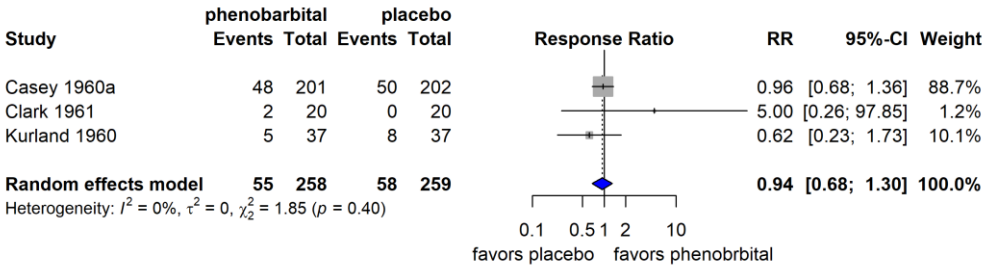


eFigure7. Sensitivity analysis using the estimate from F-values for the MSRPP scale

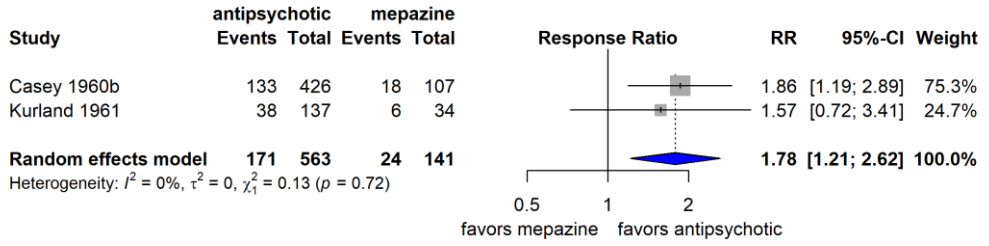


C. Post-hoc analyses of the primary outcome 'good' response

eFigure8. Phenobarbital versus inert placebo



eFigure9. Antipsychotics (apart from promazine, mepazine) versus mepazine



4. Supplementary assessment of heterogeneity for overall efficacy

Post-hoc, we evaluated the magnitude of heterogeneity for overall symptoms (primary and sensitivity analyses) by comparing the estimate τ^2 with the empirical distribution of heterogeneity found in meta-analyses (Rhodes *et al.*, 2015). According to Rhodes et al, the empirical distributions of τ^2 of standardized mean differences for mental health outcomes regarding the comparison of pharmacologic treatments versus placebo/control had a median of 0.049 IQR [0.01, 0.242].

Low heterogeneity could be considered when τ^2 was smaller than the 25% quantile of the empirical distribution (τ^2=0.01), high when τ^2 was larger than the 50% quantile (τ^2= 0.049) and moderate when τ^2 was between the 25% and 50% quantiles.

eTable6. Assessment of heterogeneity for overall symptoms

Outcome	**I^2 (%)**	**χ^2_{df}, p-value**	**τ^2**	**Heterogeneity assessment**
Primary analysis (Figure 3C)	84	18.68_3, <0.01	0.1349	*High*
Smallest SD within study (eFigure6)	48.7	5.84_3, 0.12	0.0248	*Moderate*
MSRPP SD from F-values (eFigure7)	31.6	4.39_3, 0.22	0.0123	*Low to moderate*

5. Subgroup and meta-regression analyses

The following a priori defined subgroup and meta-regression analyses were performed (not enough data were available for specific patient subgroups, i.e. treatment resistance, predominant negative symptoms, children and adolescent, as well as the type of active placebo, i.e. barbiturate or benzodiazepines):

A. Duration of follow-up

eTable7. Subgroup analysis of the primary outcome for duration of follow-up

Effect size (Response Ratio, M-H)					Heterogeneity	Test for subgroup differences	
Groups	**N**	**Point estimate**	**Lower limit of 95% CI**	**Upper limit of 95% CI**	**I^2 (%)**	**χ^2 (df)**	**p-value**
Longer-term (>3 months)	1	3.00	0.69	13.12	0.0	0.19 (1)	0.66
Shorter-term (3 weeks-3months)	5	2.12	1.27	3.51	57.1		

N: number of studies, M-H=Maentel-Haenszel, 95% CI=95% Confidence Interval, df: degrees of freedom of Q-test for subgroup differences. Only one study, Clark 1961 (Clark *et al.*, 1961), had a follow-up longer than 3 months (16 weeks).

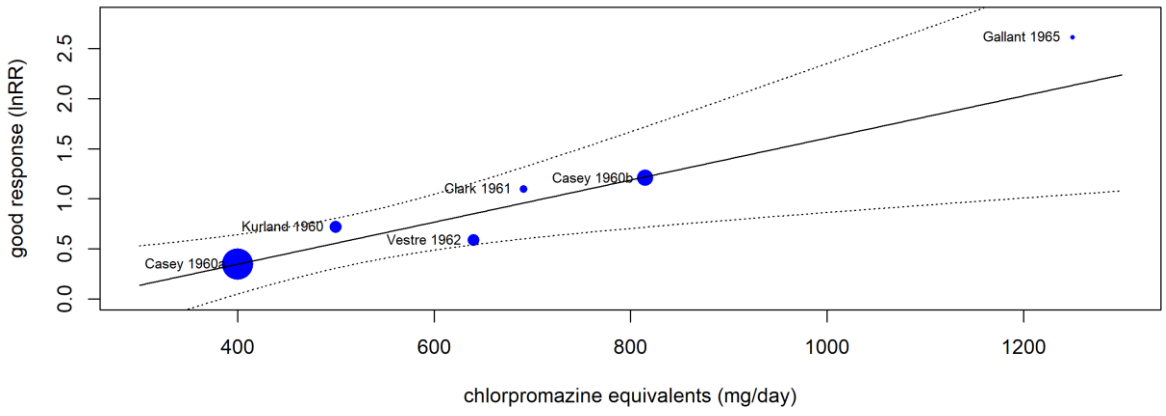
B. Daily dose (chlorpromazine equivalents)

eTable8. Meta-regression analysis of the primary outcome for daily dose in chlorpromazine equivalents

	N	**Point estimate**	**SE**	**z-test**	**Lower limit of 95% CI**	**Upper limit of 95% CI**	**p-value**
Slope	6	0.0021	0.0007	2.8653	0.0007	0.0035	**0.0042**
Intercept		-0.4946	0.3970	-1.2460	-1.2726	0.2834	0.2127

N: number of studies, SE: standard error, 95%CI=95% Confidence Interval

eFigure10. Meta-analytic scatter plot for 'good' response and daily dose in chlorpromazine equivalents



Meta-analytic scatter plot of response ratios (presented as lnRR) and chlorpromazine equivalents (in mg/day). The meta-regression line and its 95% confidence intervals are presented.

A dose-response meta-analysis estimated the dose-response curve of antipsychotic drugs (Davis and Chen, 2004). In general, drugs follows a sigmoid dose response curve when efficacy is plotted against log [dose]. This curve shows a minimal response at low doses and a log-linear part followed by an asymptotic flattening at a plateau. For chlorpromazine, the ED50 (the dose with 50% of the maximum efficacy) is estimated to be at 150mg/day, while

the near-maximal effective dose at 400-450mg/day with a plateau at about 400-800mg/day (Davis and Chen, 2004).

Therefore, we would like to stress out that our meta-regression analysis cannot provide reliable information about the dose-response relationships of antipsychotic drugs and it should be interpreted with most caution:

1. Meta-regression analyses are not protected by randomization and hence other factors could have confounded the results. In addition, conservative estimates of standard deviations (see eAppendix-5.3B) in three studies (Casey *et al.*, 1960a; Kurland *et al.*, 1961; Vestre *et al.*, 1962) could have underestimated response ratios in comparison to the other three studies (see eAppendix-5.3B).
2. The analysis was based only on six studies (potential chance findings).
3. Only one study had fixed dose schedules (Casey *et al.*, 1960a), and flexible dose studies could overestimate the near-maximal effective doses (Davis and Chen, 2004).
4. Meta-regressions of aggregated data are prone to ecological fallacy.
5. Chlorpromazine equivalents were calculated according to the international consensus of Gardner et al (Gardner *et al.*, 2010). This methodology similar to most of the methods of calculating dose equivalents uses linear interpolation (a simple proportion of equivalent doses is used across all dose ranges) ignoring dose-response curves of antipsychotic drugs (Davis and Chen, 2004). In addition, the confidence on clinical equivalent doses in the consensus was low for some drugs, e.g. trifluperidol, prochlorperazine and trifluopromazine (Gardner *et al.*, 2010) as well as the dose-response curves of these drugs have not been studied.
6. There was an outlier study of Gallant 1965 (Gallant *et al.*, 1965) , which might have influenced the results. This study compared trifluperidol, trifluoperazine and phenobarbital and no participant on phenobarbital had a response.

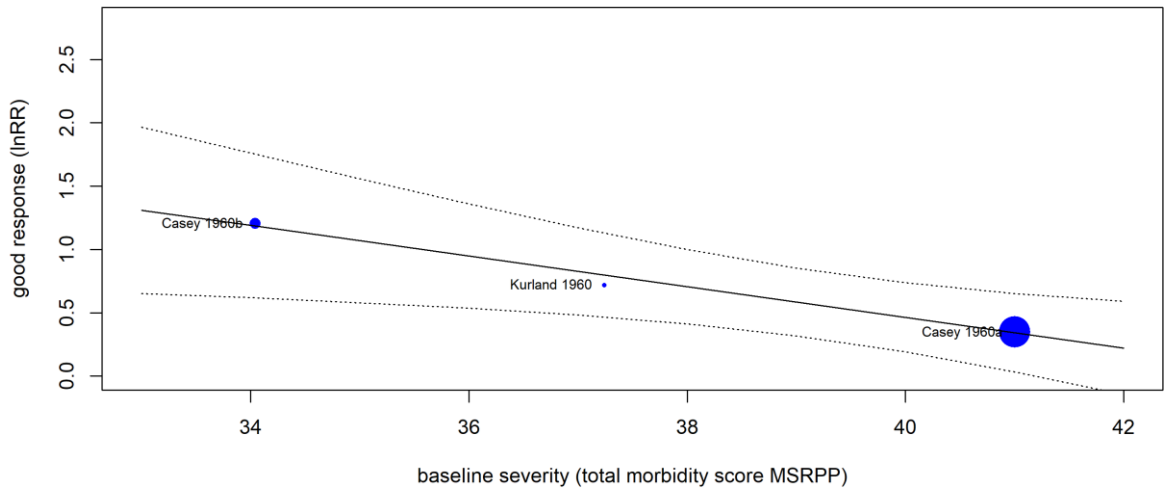
C. Baseline severity (MSRPP)

eTable9. Meta-regression analysis of the primary outcome for baseline severity (total MSRPP)

	N	Point estimate	SE	z-test	Lower limit of 95% CI	Upper limit of 95% CI	p-value
Slope	3	-0.1209	0.0486	-2.4886	-0.2161	-0.0257	**0.0128**
Intercept		5.3	1.9146	2.7682	1.5474	9.0526	0.0056

N: number of studies, SE: standard error, 95%CI=95% Confidence Interval

eFigure11. Meta-analytic scatter plot for 'good' response and baseline severity (total MSRPP)



Meta-analytic scatter plot of response ratios (presented as lnRR) and baseline severity (in total score of MSRPP). The meta-regression line and its 95% confidence intervals are presented.

In contrast to our results, a secondary analysis of the included study Casey 1960b (Casey *et al.*, 1960b) suggested that patients with a higher baseline severity have a greater response to phenothiazines (Marks, 1963). This is also in accordance with a recent individual-participant-data meta-analysis of six placebo-controlled studies in schizophrenia that found larger effect sizes with greater baseline severity (Furukawa *et al.*, 2015). Therefore, this meta-regression should also be interpreted with most caution (similar to the meta-regression of dose, eAppendix-5.5B), since it based only on three studies, and aggregated data (ecological fallacy) as well as conservative estimates of standard deviations and response rates were used (see eAppendix-5.3B).

6. References

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eAppendix 6. Strength of the evidence according to GRADE

eAppendix 6. Strength of evidence according to GRADE

Strength of evidence for the primary outcome was rated according to GRADE (Grading of Recommendations, Assessment, Development and Evaluations) (Schünemann *et al.*, 2013).

1. Antipsychotic drugs versus barbiturates

Antipsychotic drugs compared to barbiturates for schizophrenia

Patient or population: schizophrenia

Setting: any setting

Intervention: antipsychotic drugs

Comparison: barbiturates

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Response with barbiturates	**Response with antipsychotic drugs**				
'Good' response follow up: range 6 weeks to 16 weeks	168 per 1.000	**362 per 1.000** (229 to 574)	**RR 2.15** (1.36 to 3.41)	1302 (6 RCTs)	⨁⨁◯◯ LOW [a,b,c,d,e]	

***The response in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Response ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Risk of bias: rated as very serious; the included studies were old and published long before the CONSORT statement for RCTs. Randomization sequence generation and allocation concealment were poorly reported. Most of the studies had adequate blinding in terms of performance and detection bias. High risk of bias for incomplete outcome data (Casey *et al.*, 1960; Kurland *et al.*, 1961) or selective reporting (Gallant *et al.*, 1965; Hollister, 1972) was evident, while for the rest of the studies unclear.

b. Inconsistency: rated as not serious; some heterogeneity was present across studies (I-squared = 48.9%, p value for the chi-square test 0.08) and the direction of the effect of all studies was the same.

c. Indirectness: rated as not serious

d. Imprecision: rated as not serious; considerable number of participants (1302 for 'good' response) and the lower boundary of 95% confidence intervals does not include 1.25.

e. Publication bias: not detected; assessment of small study effects and the associated publication bias based on on the asymmetry of funnel plot cannot distinguish chance from real asymmetry when studies are fewer than 10.

eAppendix 6. Strength of evidence according to GRADE

2. Antipsychotic drugs versus benzodiazepines

Antipsychotic drugs compared to benzodiazepines for schizophrenia

Patient or population: schizophrenia

Setting: any setting

Intervention: antipsychotic drugs

Comparison: benzodiazepines

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Response with benzodiazepines	**Response with antipsychotic drugs**				
'Good' response	-	-	-	-	-	No data available regarding 'good' response.
'Any' response follow up: 4 weeks	650 per 1.000	**747 per 1.000** (533 to 1.000)	**RR 1.15** (0.82 to 1.62)	60 (1 RCT)	⨁⨁◯◯ LOW [a,b,c,d,e]	

***The response in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Response ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Risk of bias rated as serious; high risk of bias in terms of selective reporting. Unclear risk of bias in terms of random sequence generation, allocation concealment, blinding of outcome assessors and incomplete outcome data.

b. Inconsistency: rated as not serious, cannot be judged by one study

c. Indirectness: rated as not serious

d. Imprecision: rated as serious, only one small study was included (60 participants) and 95% confidence interval did not exclude the null effect or the effect to benefit (1.25).

e. Publication bias: rated as undetected; since one study was included.

3. References

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