

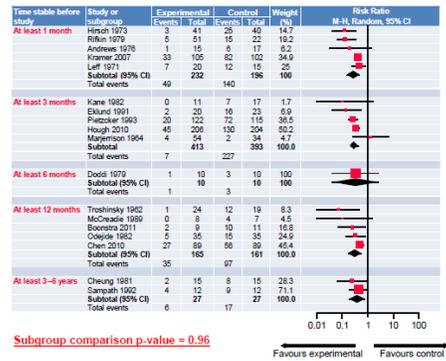
Systematic Reviews and Meta-analyses

Prof Stefan Leucht
Section for Evidence-Based Medicine
Psychiatry and Psychotherapy
Technical University of Munich
Germany



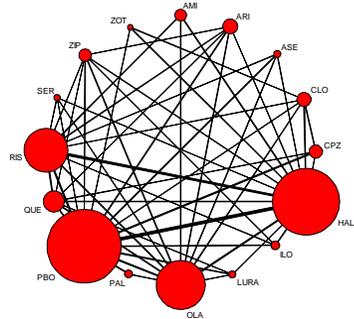
Meta-analytic methods

Cochrane Reviews Pairwise meta-analysis



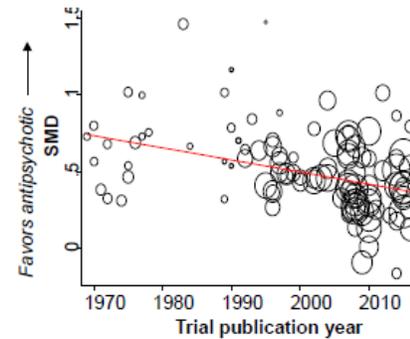
Leucht et al. Lancet 2012,
Cochr Database Syst Rev 2012

Network meta-analysis



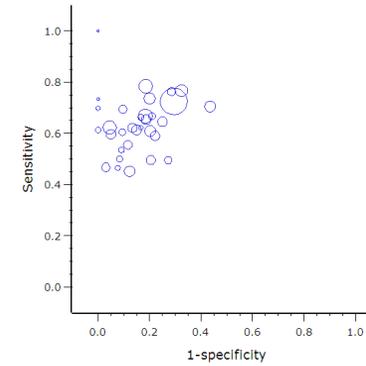
Leucht et al. Lancet 2013,
Huhn...Leucht Lancet 2019

Metaregression



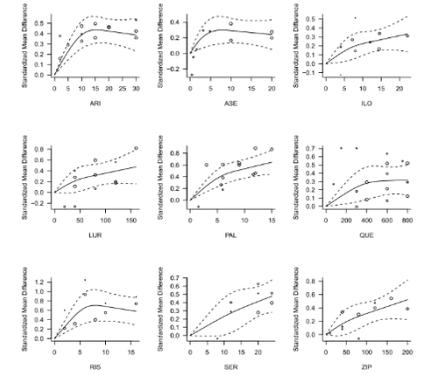
Leucht et al. Am J Psych 2017

Diagnostic Test Reviews



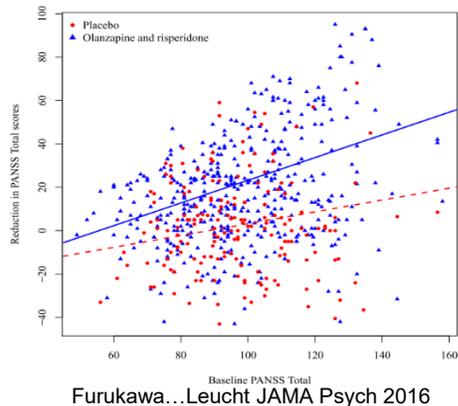
Samara...Leucht Am J Psych 2015

Dose-Response Meta-analysis



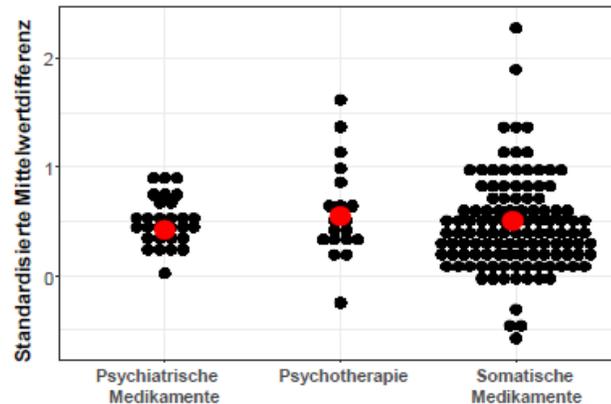
Leucht et al. Am J Psych 2020

Individual Patient Data (IPD) Meta-analyses



Furukawa...Leucht JAMA Psych 2016

Overviews of Reviews



Leucht et al. Br J Psych 2012,
Huhn...Leucht Leucht JAMA Psych 2016

Systematic Reviews of Rating Scales



Weigl...Leucht Schiz Bull 2023

Component IPD Network Meta-analyses

	Depression severity (MD of PHQ-9 scores), median (95% CrI)
Age	0.19 (-0.09 to 0.47)
Baseline depression, PHQ-9 scores	2.59 (2.32 to 2.85)
Gender*	-0.03 (-0.28 to 0.18)
Relationship†	-0.12 (-0.33 to 0.12)
Waiting component	0.42 (-0.75 to 1.53)
Non-specific treatment effects	-1.41 (-2.52 to -0.30)
Psychoeducation about depression	0.02 (-0.86 to 0.93)
Cognitive restructuring	0.30 (-0.87 to 1.41)
Behavioural activation	-1.83 (-2.90 to -0.80)
Interpersonal skills training	-0.54 (-1.59 to 0.52)
Problem solving	-0.64 (-1.41 to 0.09)
Relaxation	1.20 (0.17 to 2.27)
Third-wave components	-0.53 (-1.55 to 0.49)
Behaviour therapy for insomnia	-1.82 (-3.92 to 0.26)
Relapse prevention	0.35 (-0.69 to 1.32)
Homework required	0.31 (-0.69 to 1.35)
Initial face-to-face contact	0.85 (-1.80 to 3.41)
Automated encouragement to proceed with iCBT	-0.26 (-1.13 to 0.60)
Human encouragement to proceed with iCBT	-0.29 (-1.17 to 0.58)
Therapeutic guidance for iCBT	0.01 (-0.88 to 0.89)

Furukawa...Lancet Pych 2021

Definitions

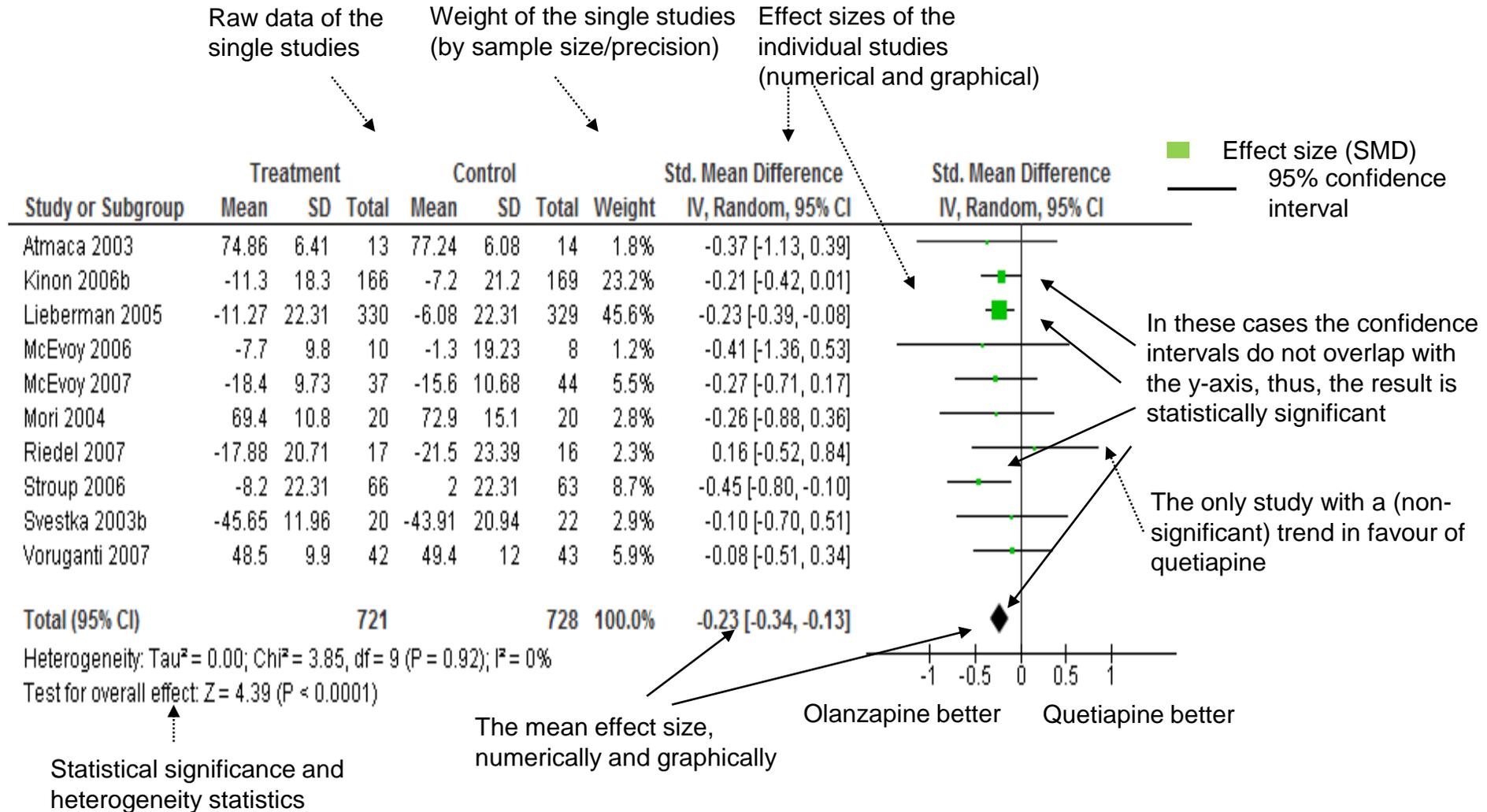
- **Systematic Review:** Means the systematic approach in terms of literature search, selection, presentation and analysis of the data
- **Meta-analysis:** Means the mathematical combination of the results of different studies on one question



<https://schizophrenia.cochrane.org/>

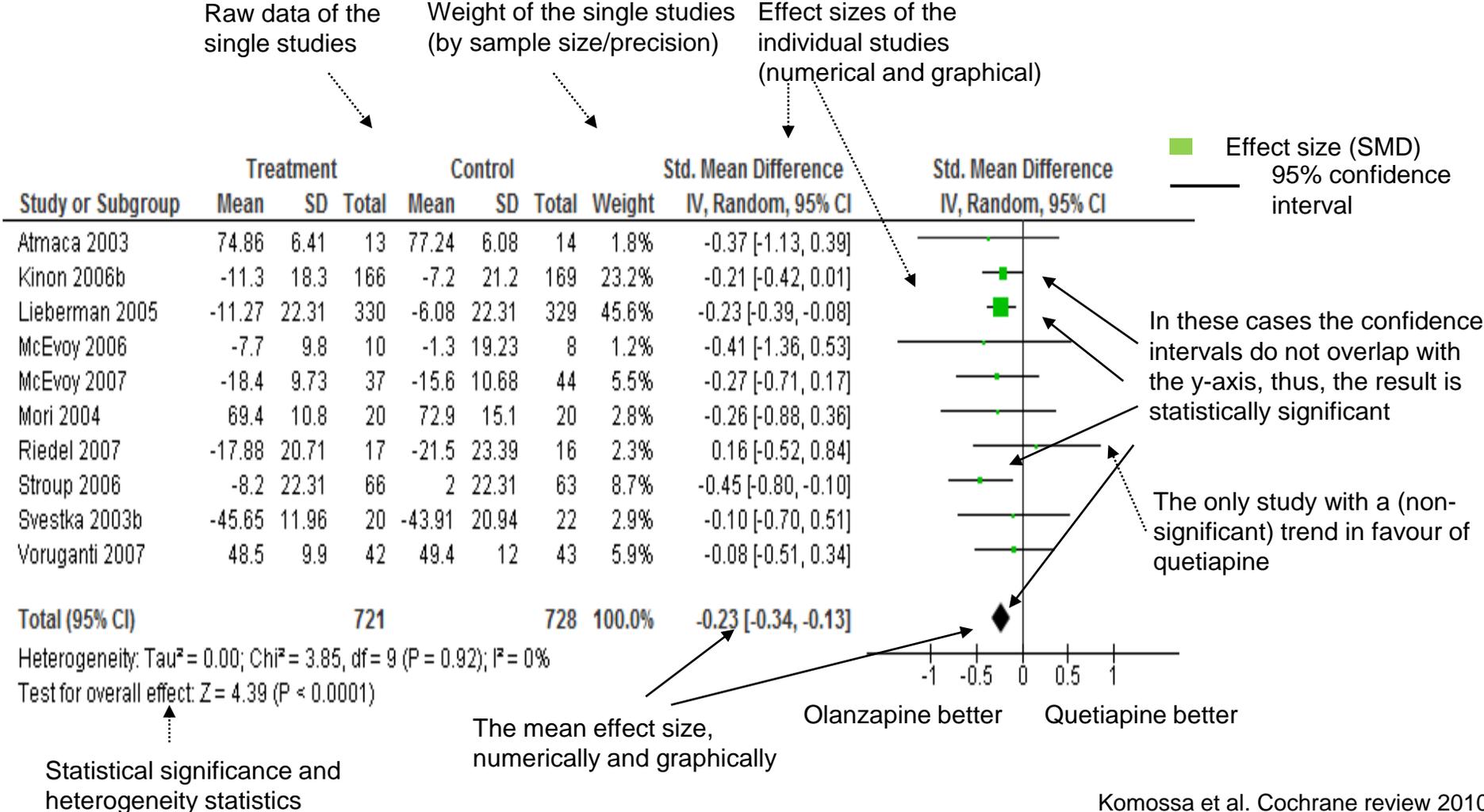
Olanzapin versus Quetiapin for Schizophrenia

- Efficacy -



How to read forest plots

Rule of thumb by Cohen for the interpretation of effect sizes:
 0.20 = small difference
 0.50 = medium difference
 0.80 = large difference between interventions



Heterogeneity

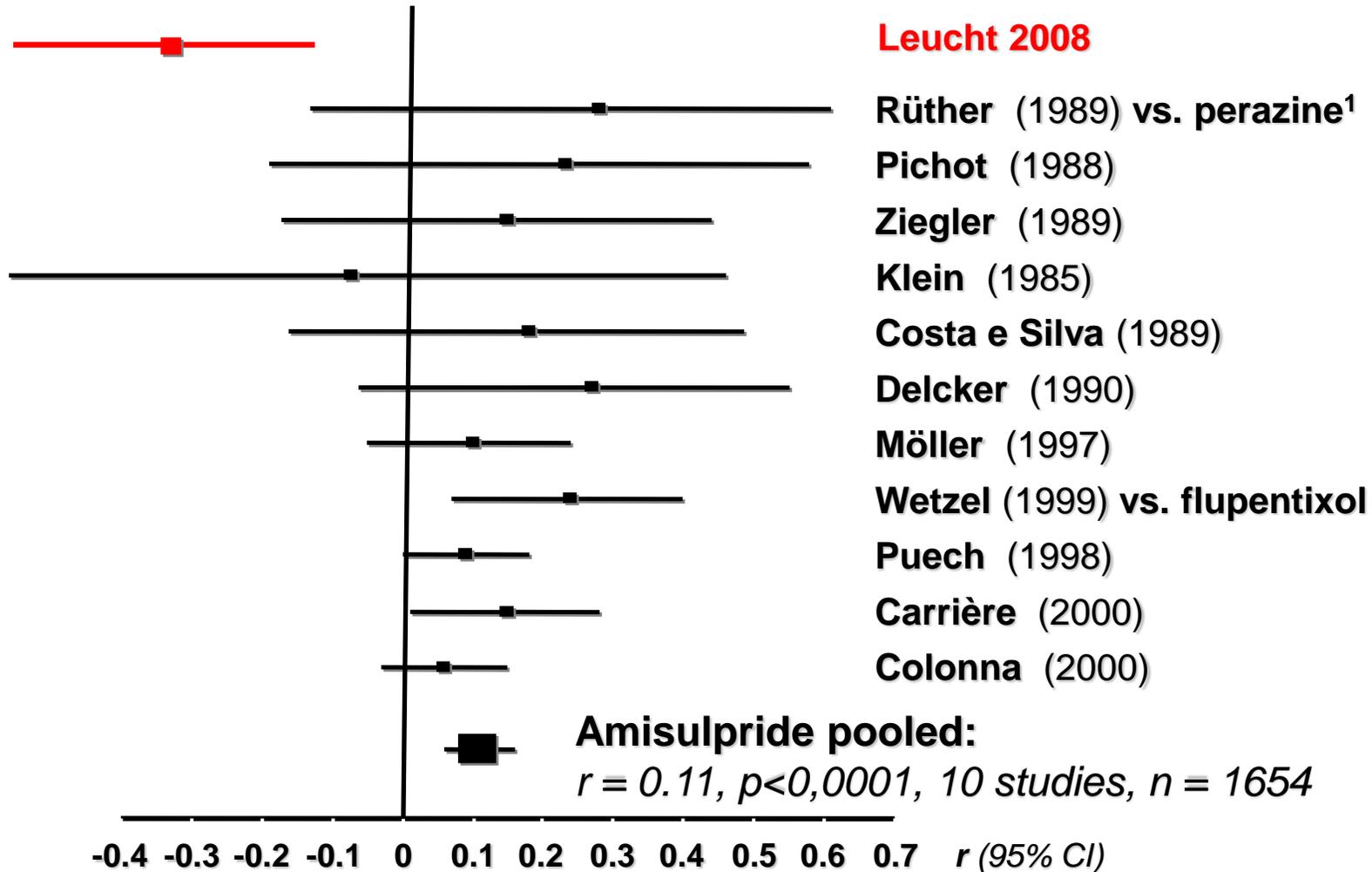
□ I^2 Statistic:

Quantitative, how much heterogeneity 0%-100%, usually 50% considerable heterogeneity

□ Chi-square test:

Likelihood of heterogeneity, usually $p < 0.1$ means heterogeneity

BPRS: Amisulpride vs. typical antipsychotics



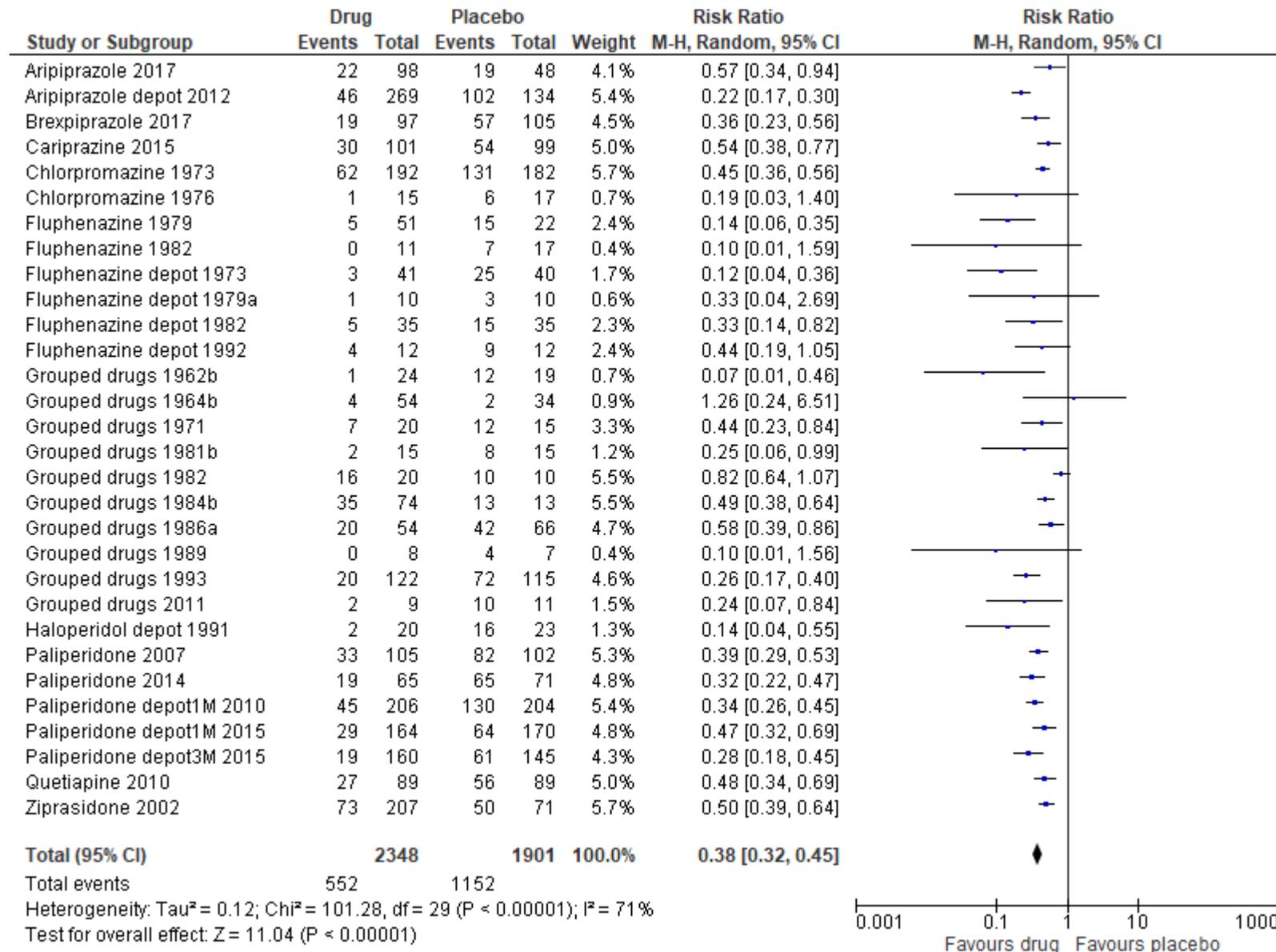
¹ endpoint analysis, not used for mean effect size

Heterogeneous?

Yes

No

Antipsychotics vs Placebo for relapse prevention of antipsychotics



Heterogeneous?

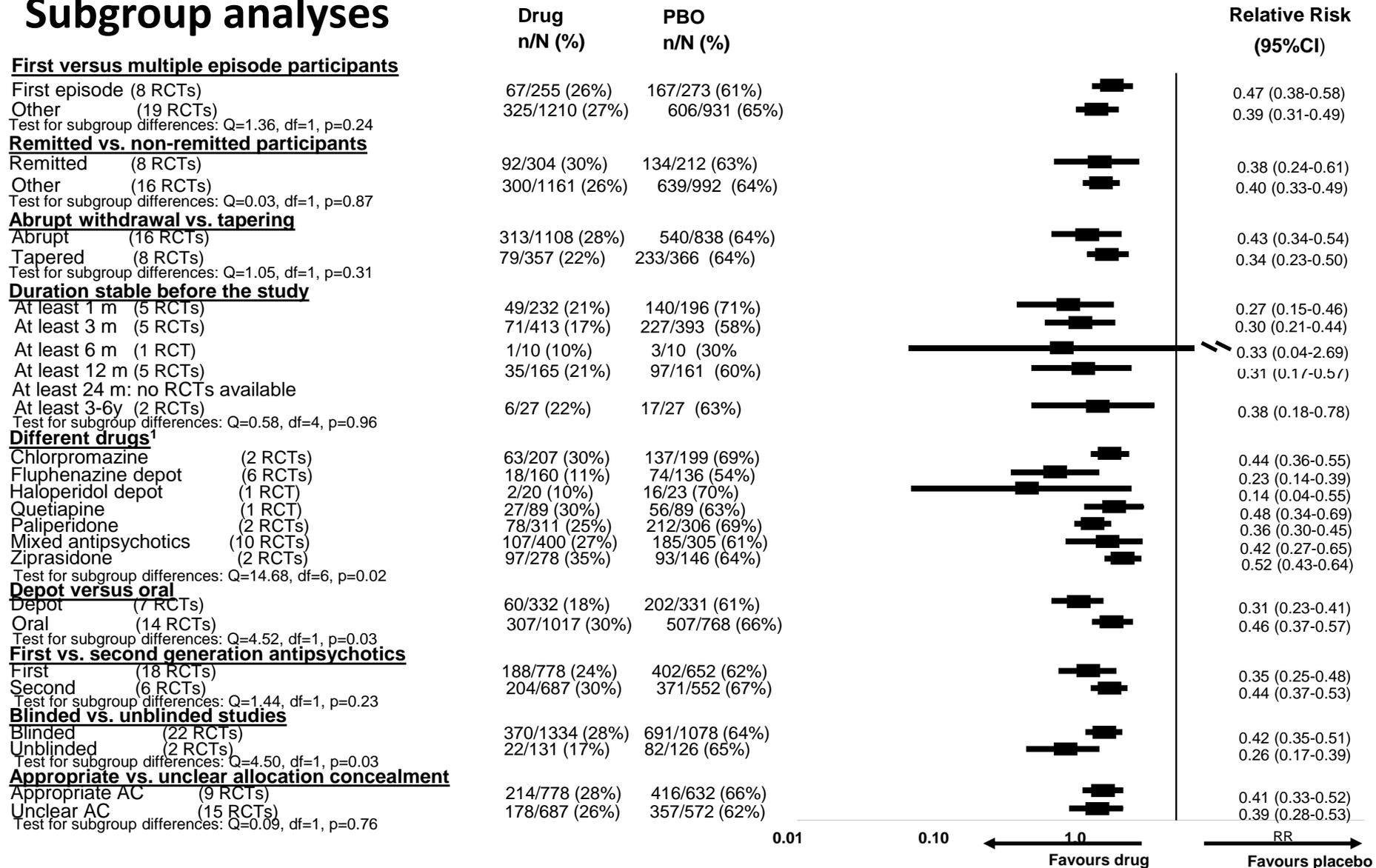
Yes

No

Subgroup analysis and meta-regression

Antipsychotics vs Placebo for relapse prevention of antipsychotics

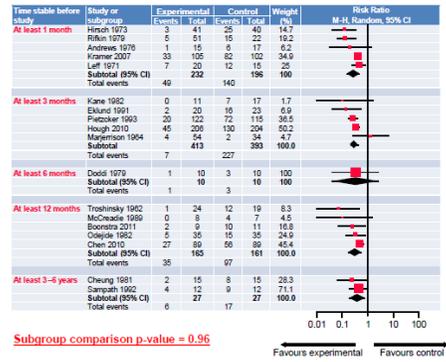
Subgroup analyses



The DerSimonian and Laird random effects model was used throughout where the weights for the risk ratio were calculated using the Mantel-Haenszel method, PBO = placebo, n = number of participants relapsed, N = total number of patients, RCTs = number of included randomised controlled trials, CI = confidence interval, m= months, y= years, AC= allocation concealment, ** p<0.001; ¹excluding the group „mixed antipsychotics“ does not change the result

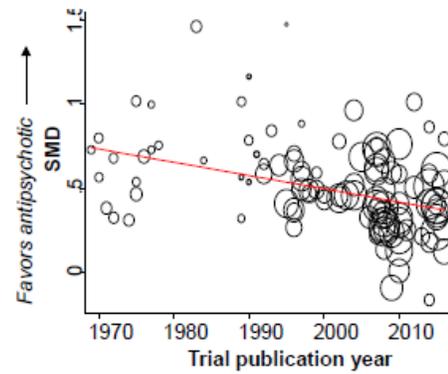
Advanced methods

Cochrane Reviews Pairwise meta-analysis



Leucht et al. Lancet 2012,
Cochr Database Syst Rev 2012

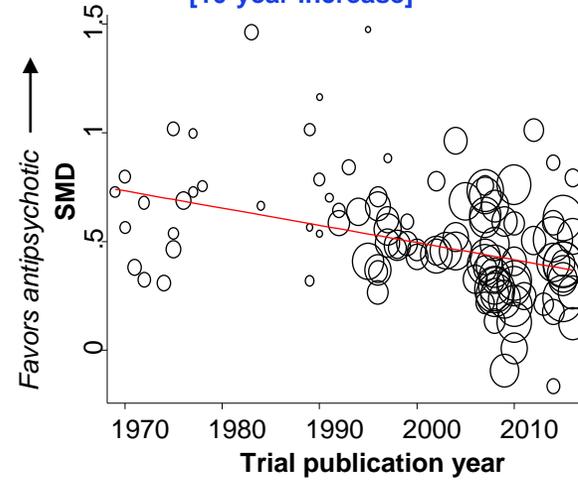
Metaregression

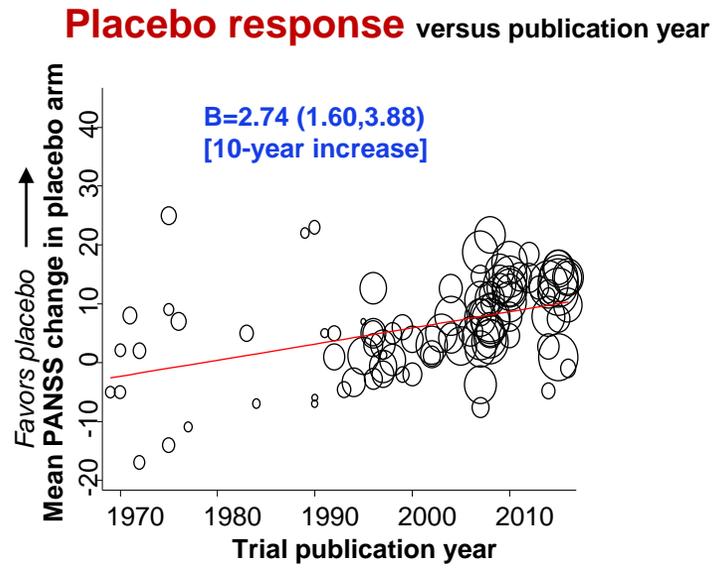
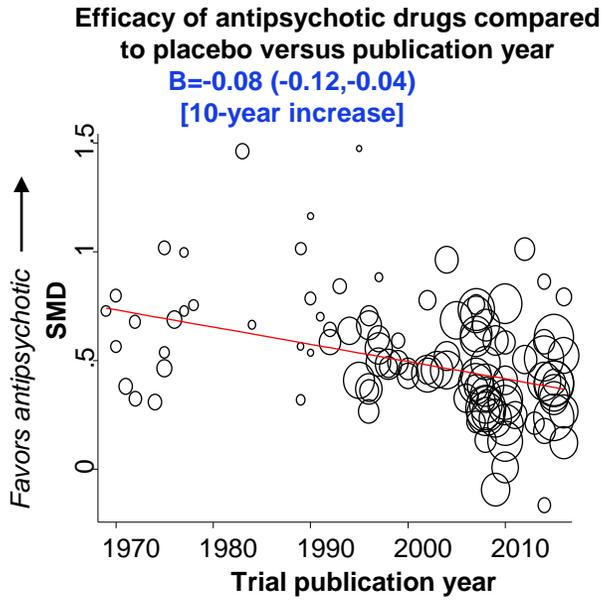


Leucht et al. Am J Psych 2017

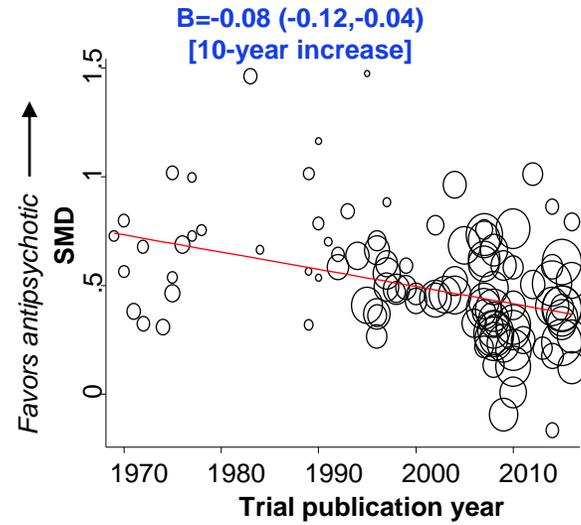
Efficacy of antipsychotic drugs compared to placebo versus publication year

$B = -0.08$ (-0.12, -0.04)
[10-year increase]

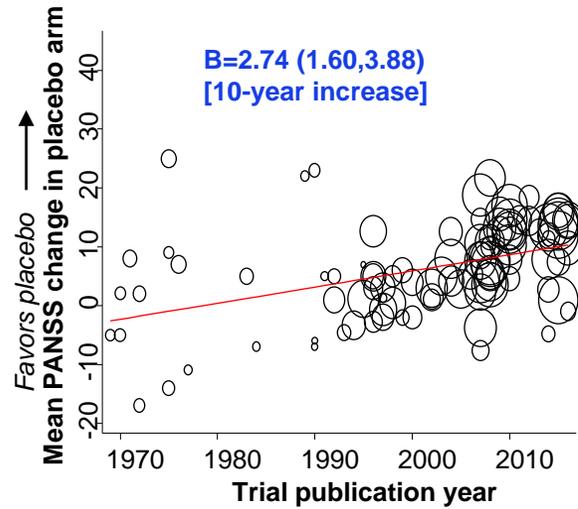




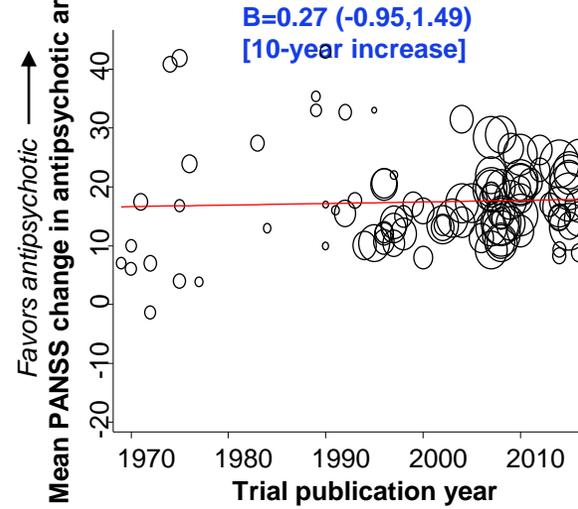
Efficacy of antipsychotic drugs compared to placebo versus publication year



Placebo response versus publication year



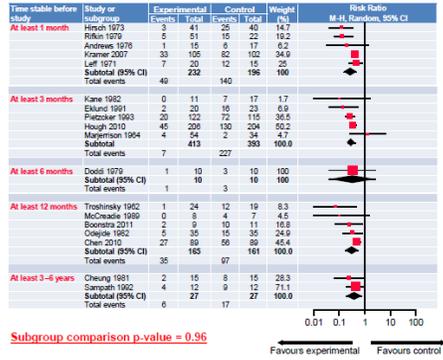
Drug response versus publication year



Network meta-analyses

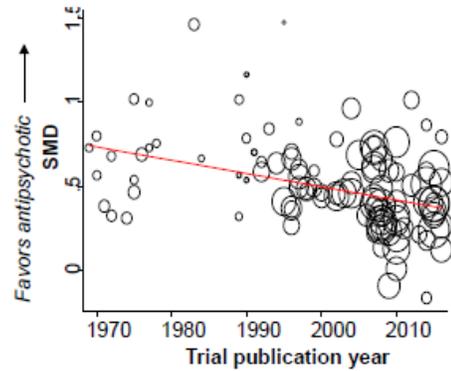
Advanced methods

Cochrane Reviews Pairwise meta-analysis



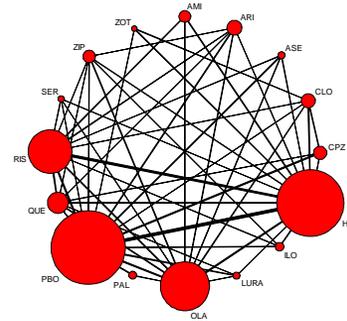
Leucht et al. Lancet 2012,
Cochr Database Syst Rev 2012

Metaregression



Leucht et al. Am J Psych 2017

Network meta-analysis



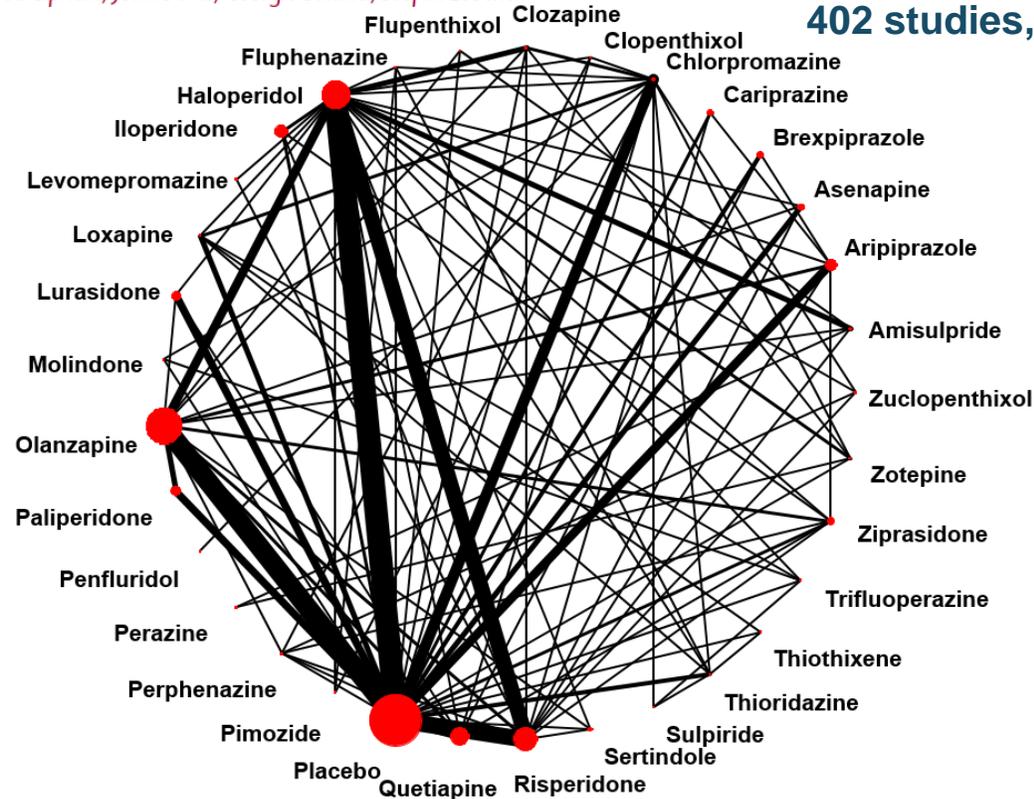
Leucht et al. Lancet 2013,
Huhn...Leucht Lancet 2019

Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis

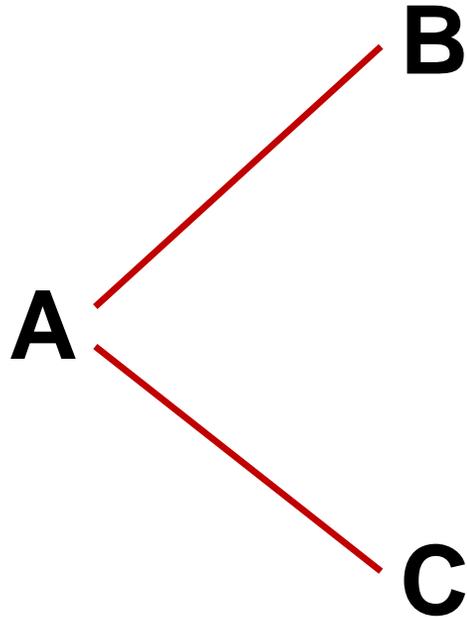


Maximilian Huhn, Adriani Nikolakopoulou, Johannes Schneider-Thoma, Marc Krause, Myrto Samara, Natalie Peter, Thomas Arndt, Lio Bäckers, Philipp Rothe, Andrea Cipriani, John Davis, Georgia Salanti, Stefan Leucht

402 studies, 53,463 participants

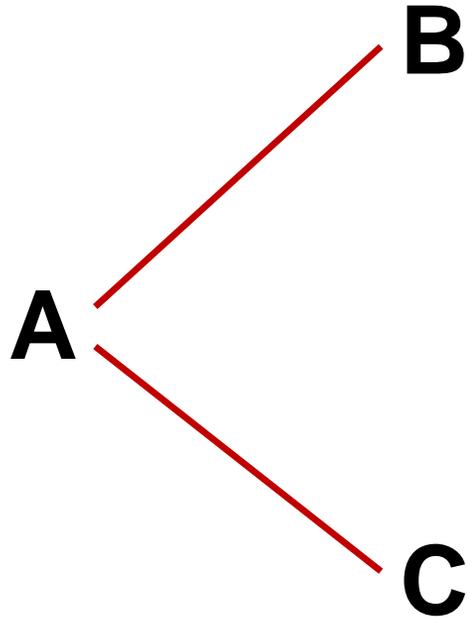


Prinzip der Netzwerkmetaanalyse

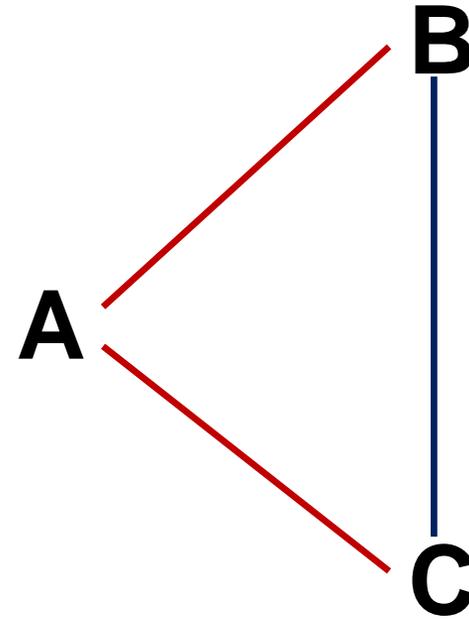


There are trials for A vs B and A vs C but none for B vs C

Prinzip der Netzwerkmetaanalyse



There are trials to compare A vs B and A vs C, but none to compare B vs C



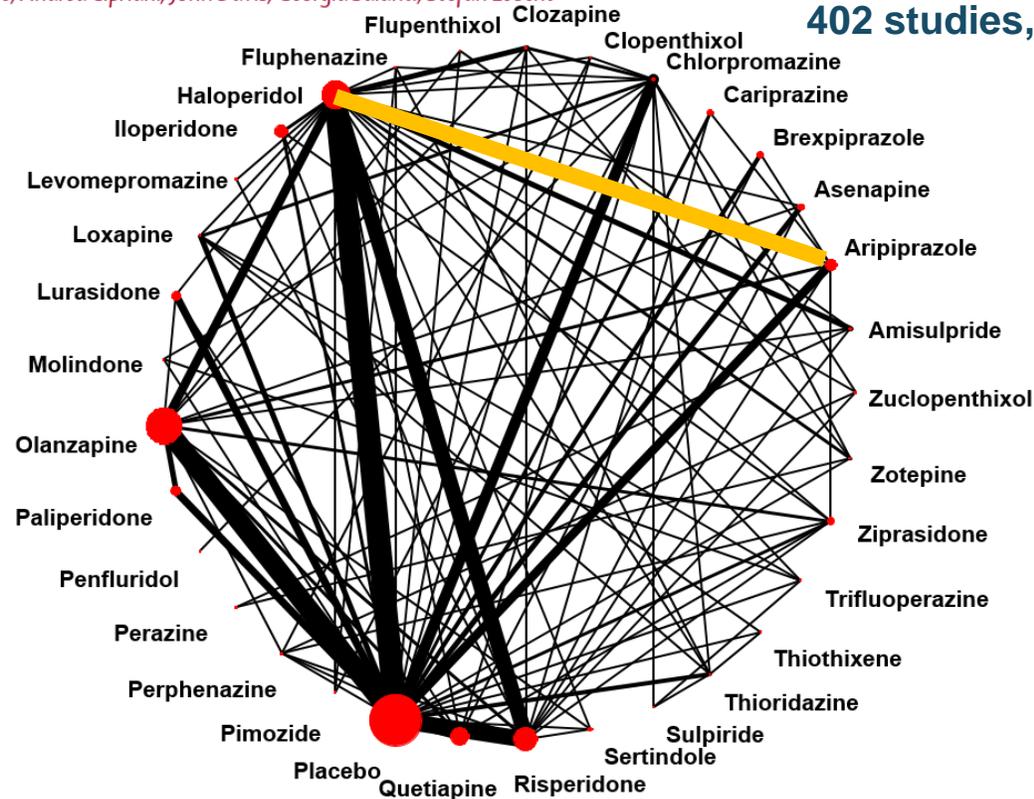
Trial results to compare B vs C can be estimated from those of A vs B and A vs C

Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis



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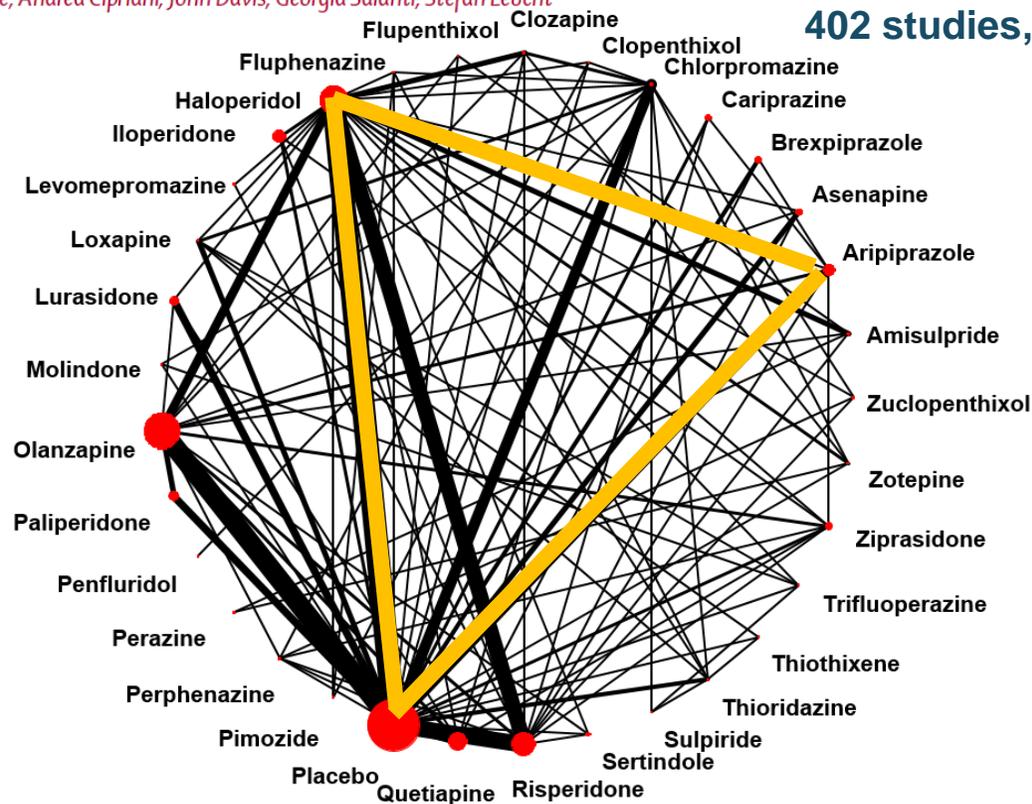


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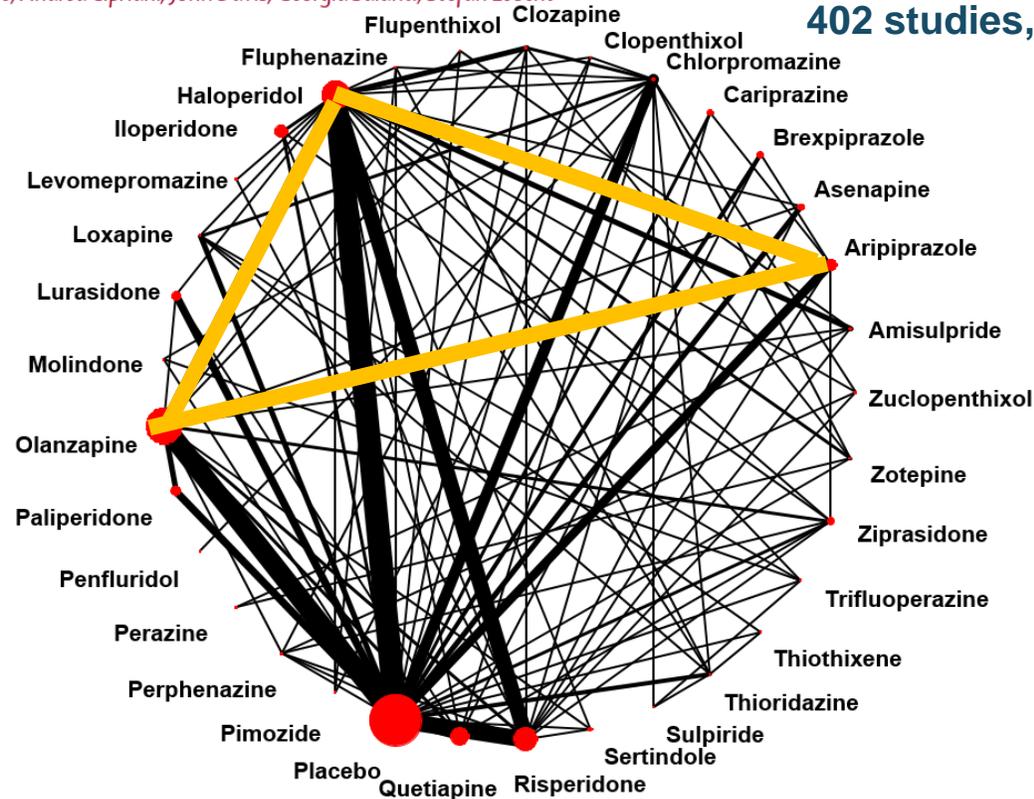


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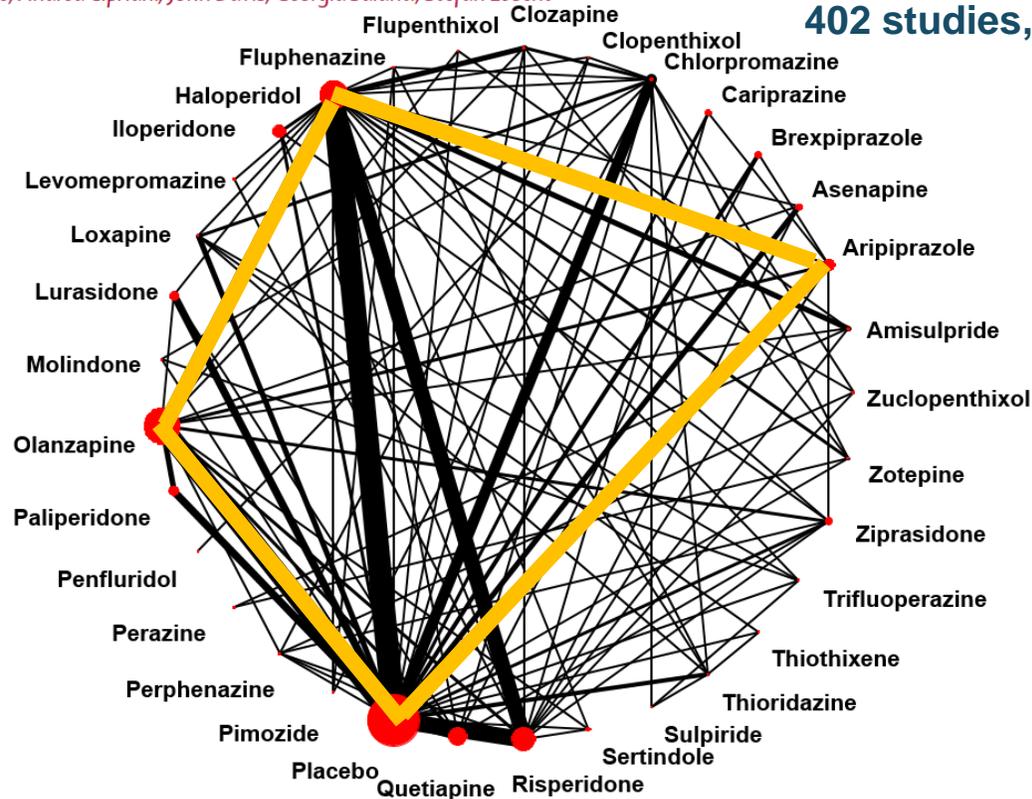


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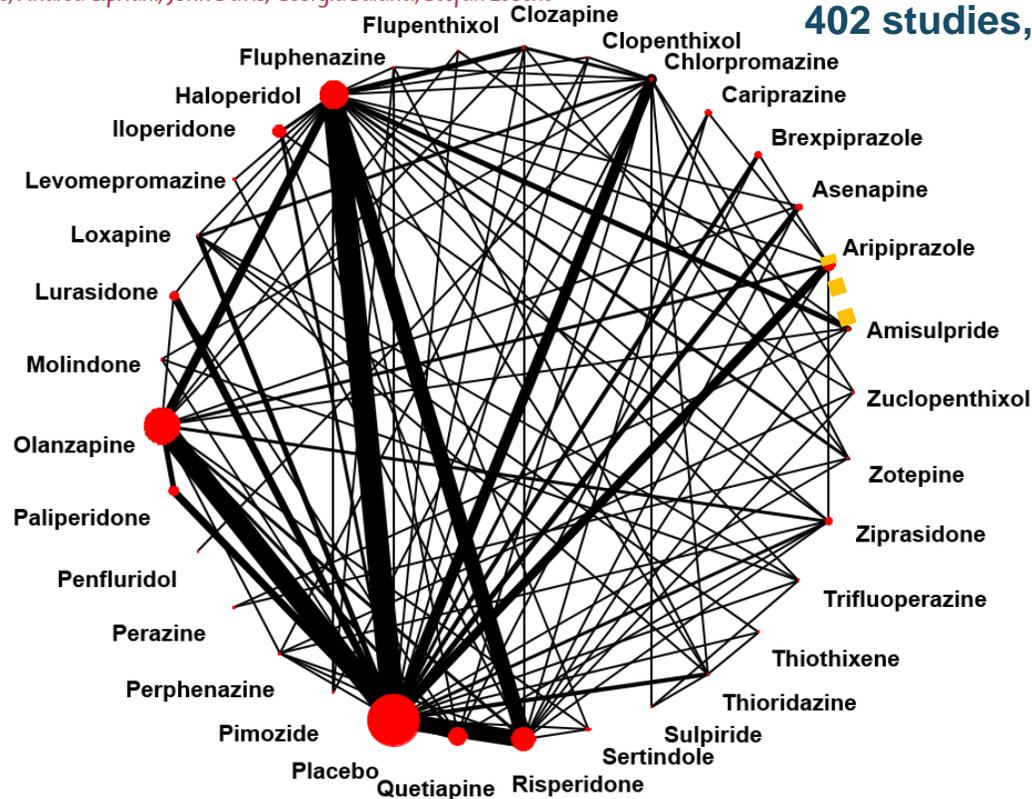


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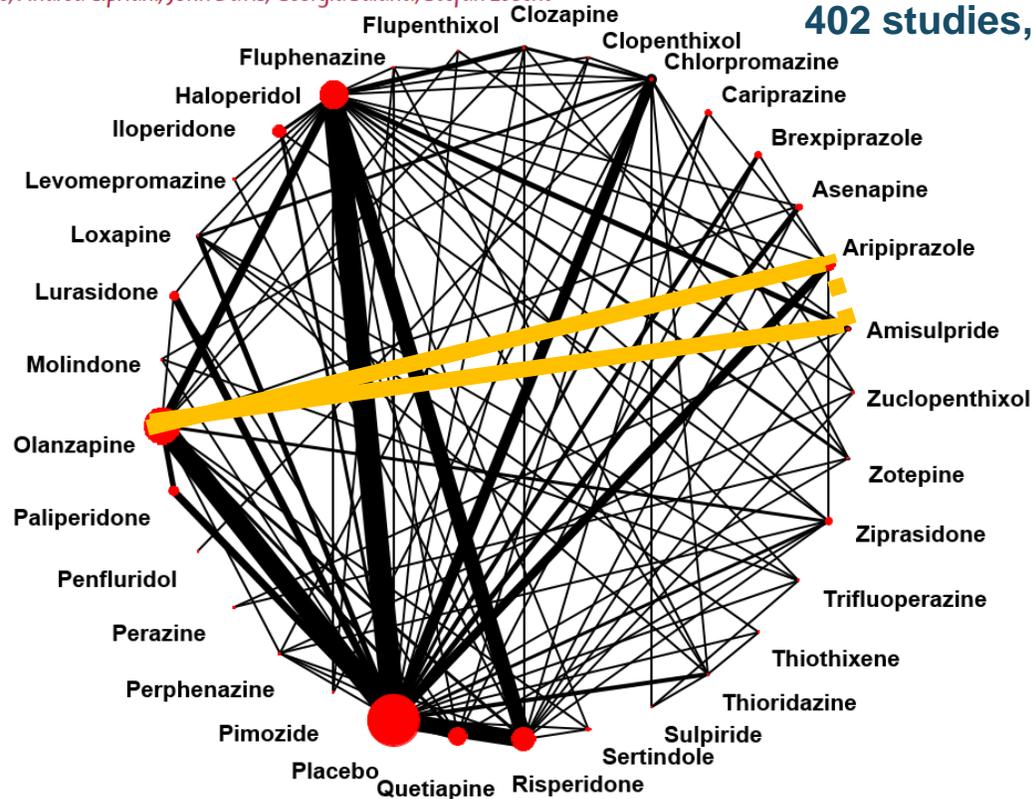


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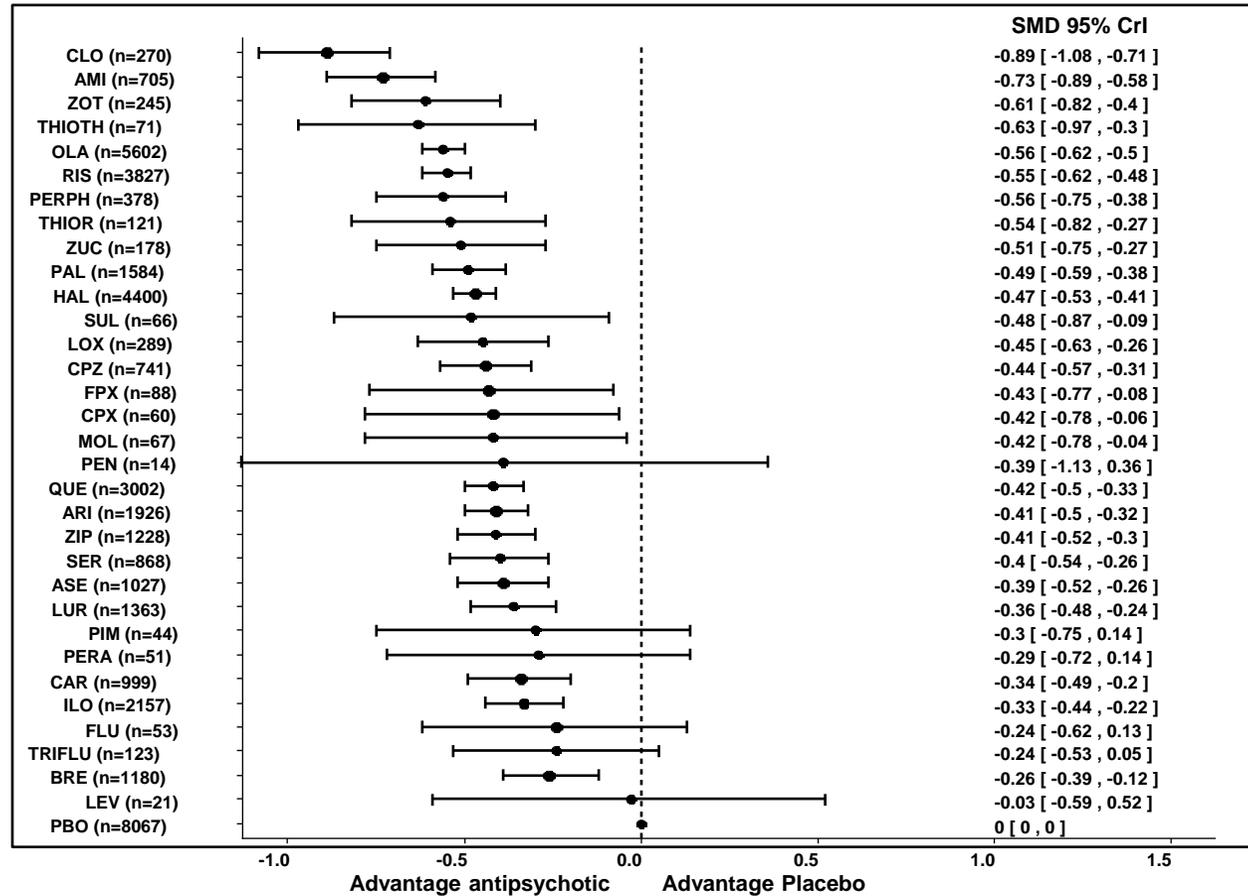
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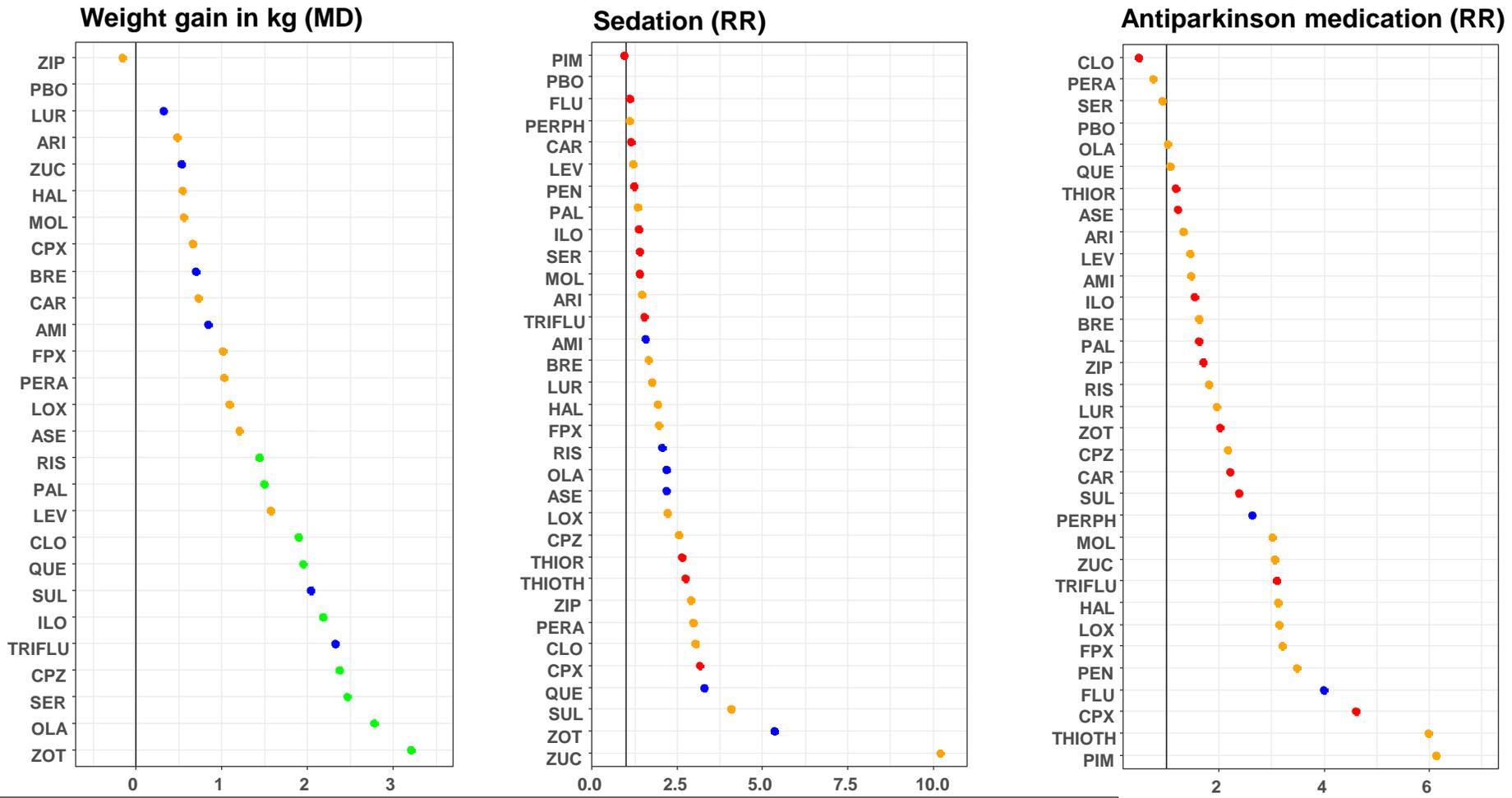
Efficacy

Reduction of PANSS or BPRS total score (N=218, n=40815)



SMD = standardised mean difference, N=number of studies, n= number of patients

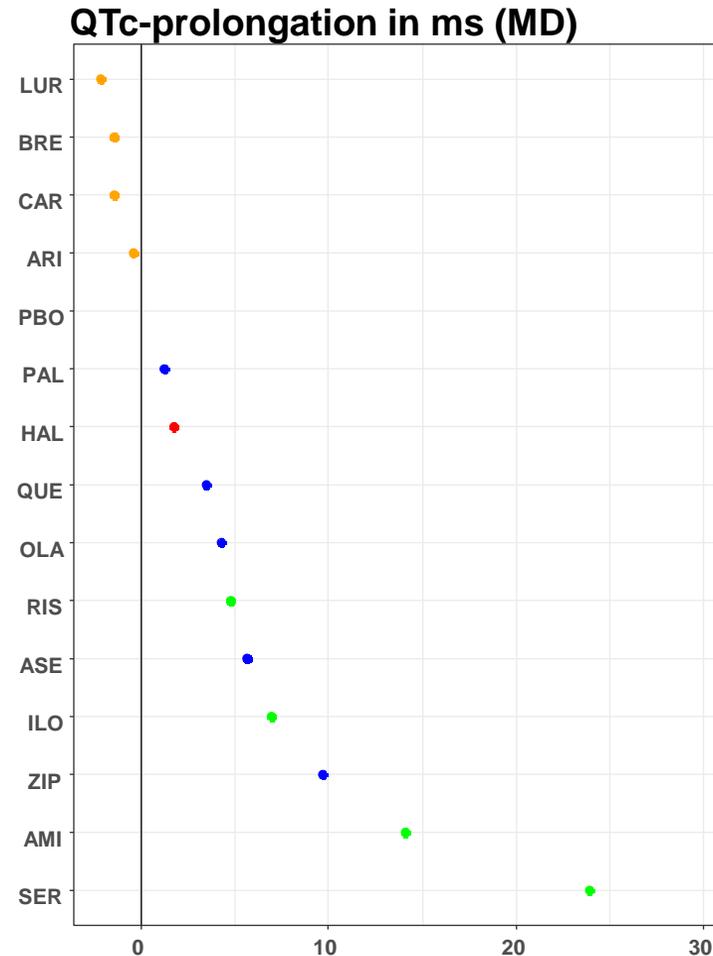
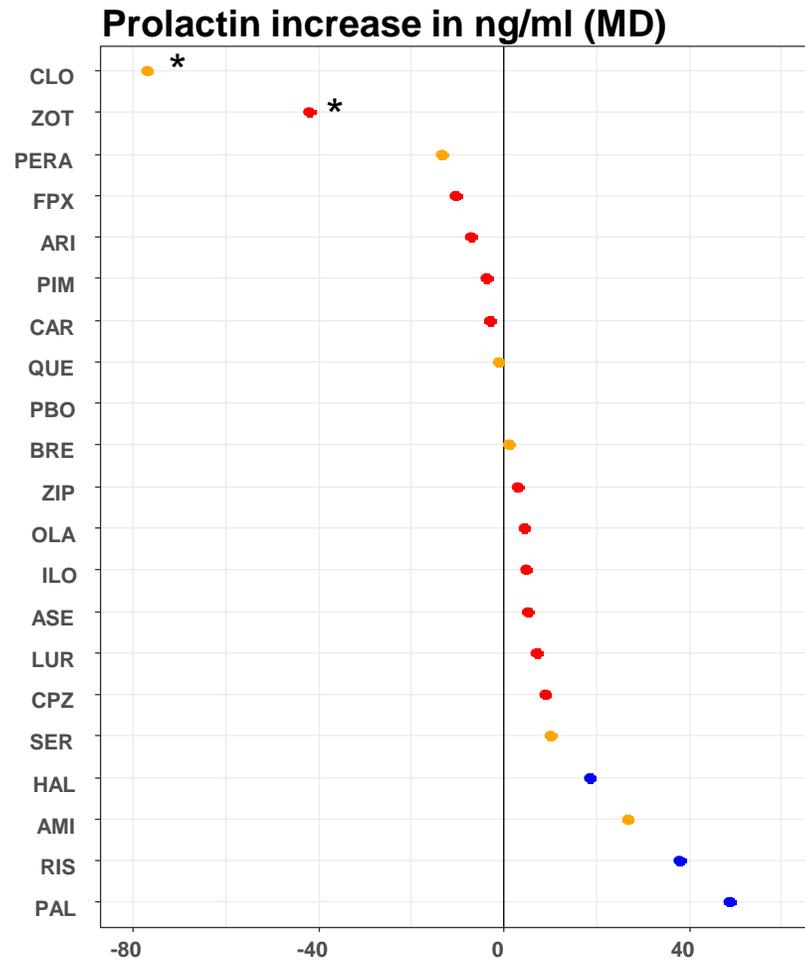
Side effects I



Confidence in Network Meta-Analysis (CINeMA): ● high ● moderate ● low ● very low

MD=Mean Difference, RR=Relative Risk

Side effects II



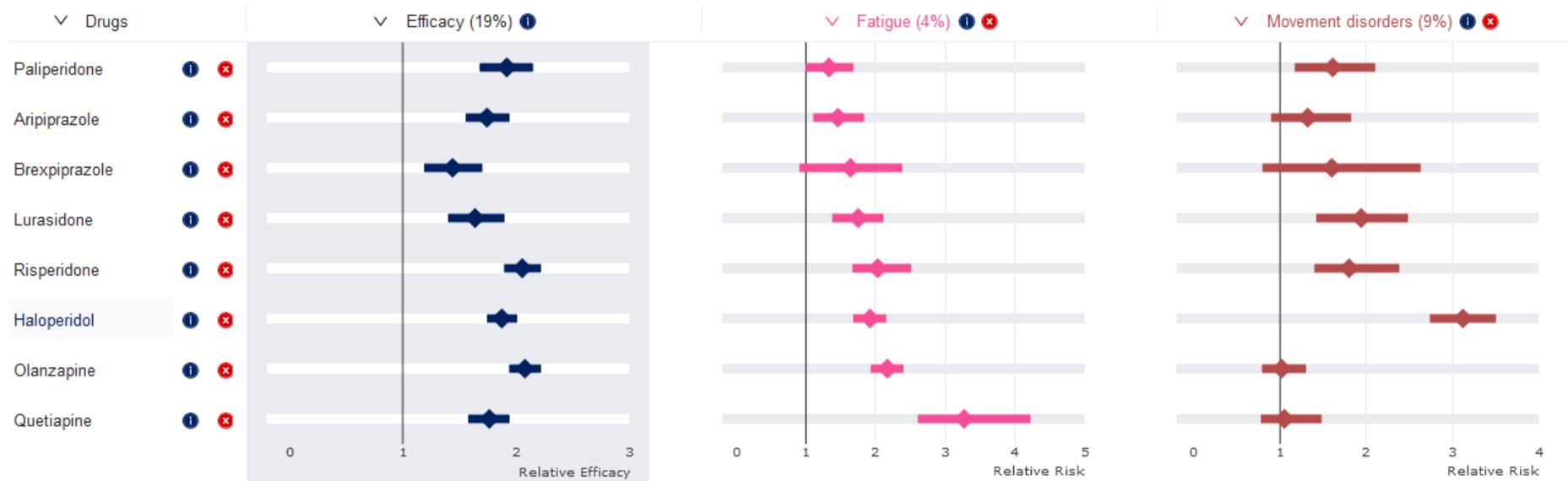
Confidence in Network Meta-Analysis (CINeMA): ● high ● moderate ● low ● very low

MD=Mean difference, ms=milliseconds, *=Clozapine and Zotepine are based on two studies with extreme results Huhn,..., Leucht Lancet 2019

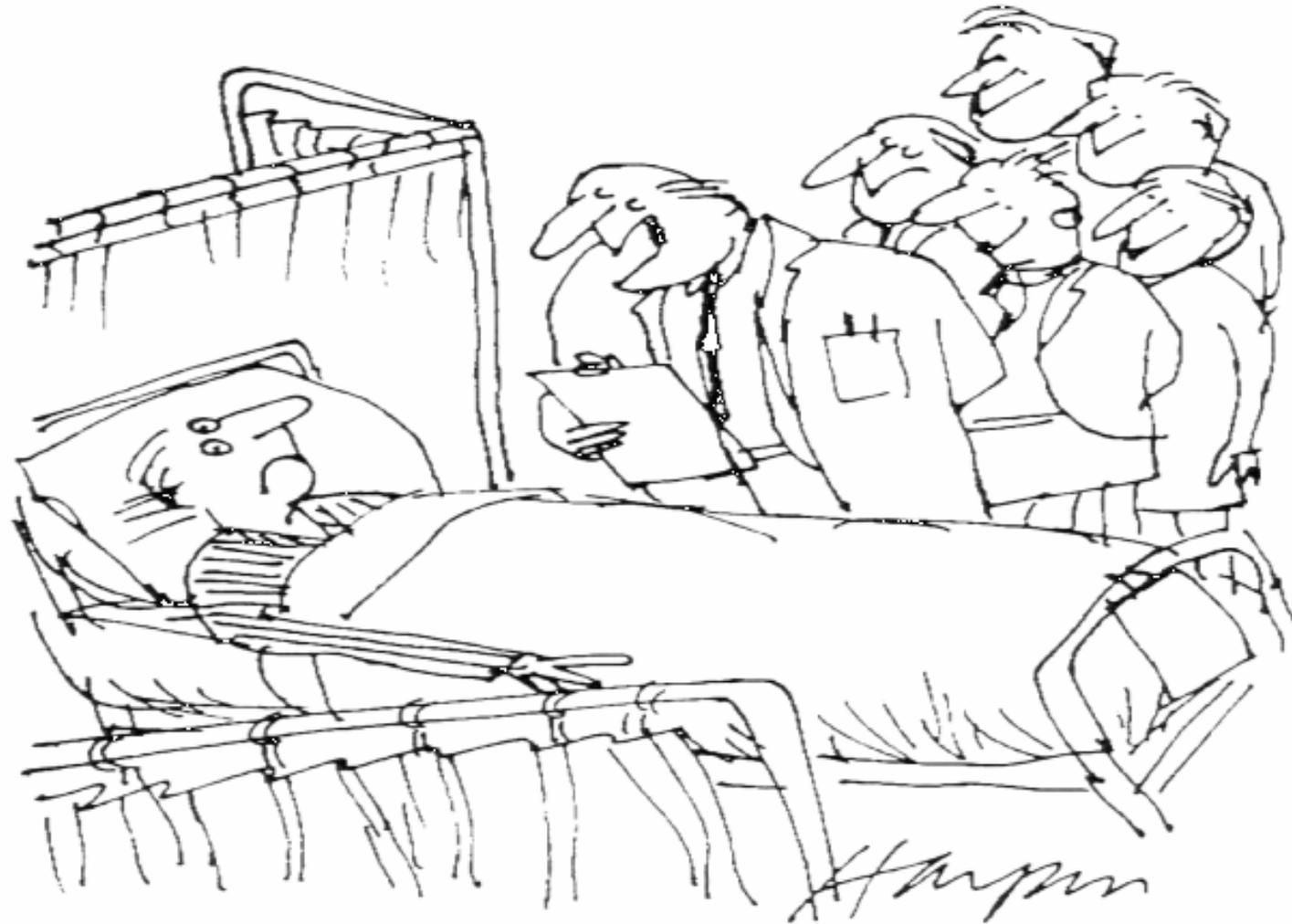
Shared Decision Making Assistant SMDA

<https://ebmpp.org/de/tools/sdma-app>

- Anticholinergic side effects
- Fatigue
- Hyperprolactinemia
- Movement disorders
- Restless legs
- Weight gain



Caricature of the paternalistic model

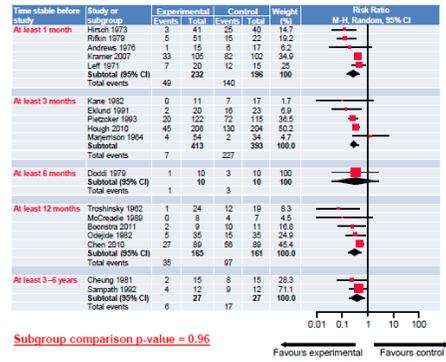


*"When we want your opinion,
we'll give it to you"*

Individual patient data meta-analysis (IPD)

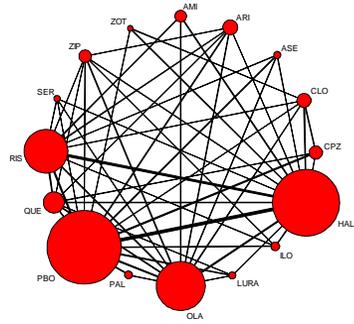
Advanced methods

Cochrane Reviews Pairwise meta-analysis



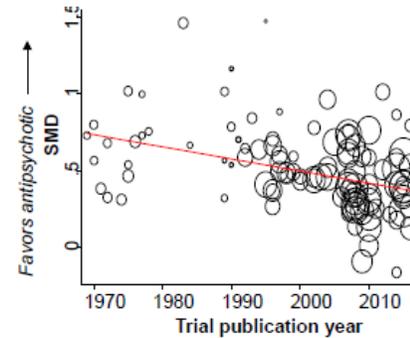
Leucht et al. Lancet 2012,
Cochr Database Syst Rev 2012

Network meta-analysis



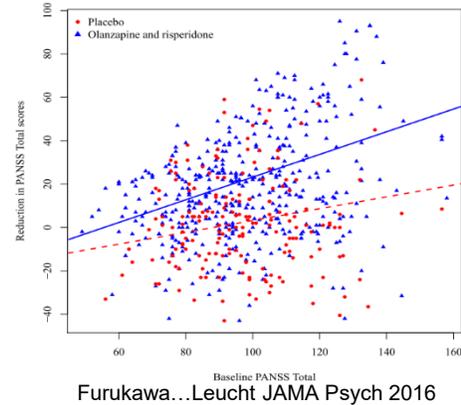
Leucht et al. Lancet 2013,
Huhn...Leucht Lancet 2019

Metaregression



Leucht et al. Am J Psych 2017

Individual Patient Data (IPD) Meta-analyses



Furukawa...Leucht JAMA Psych 2016

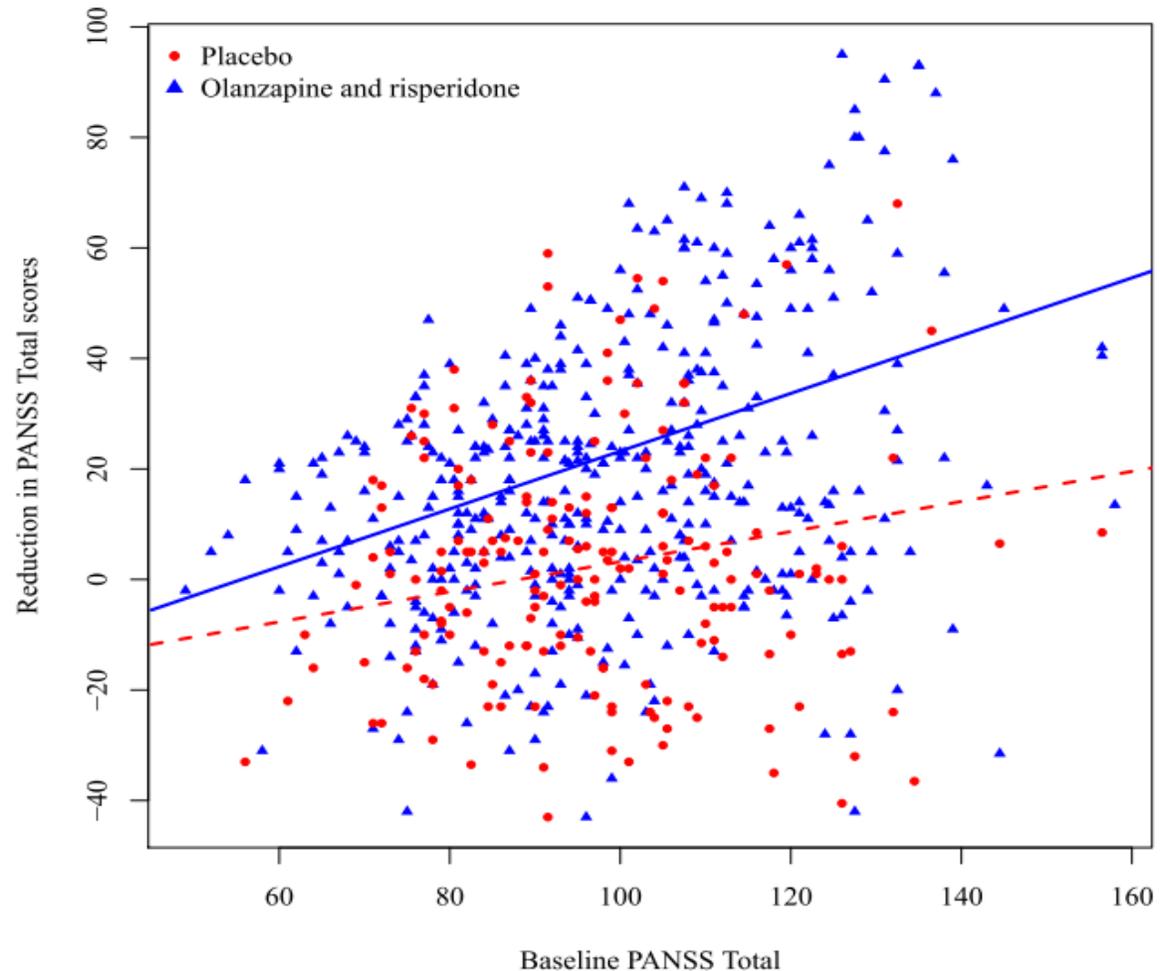
Individual patient data (IPD) meta-analysis

Are antipsychotics more effective in severely ill patients?

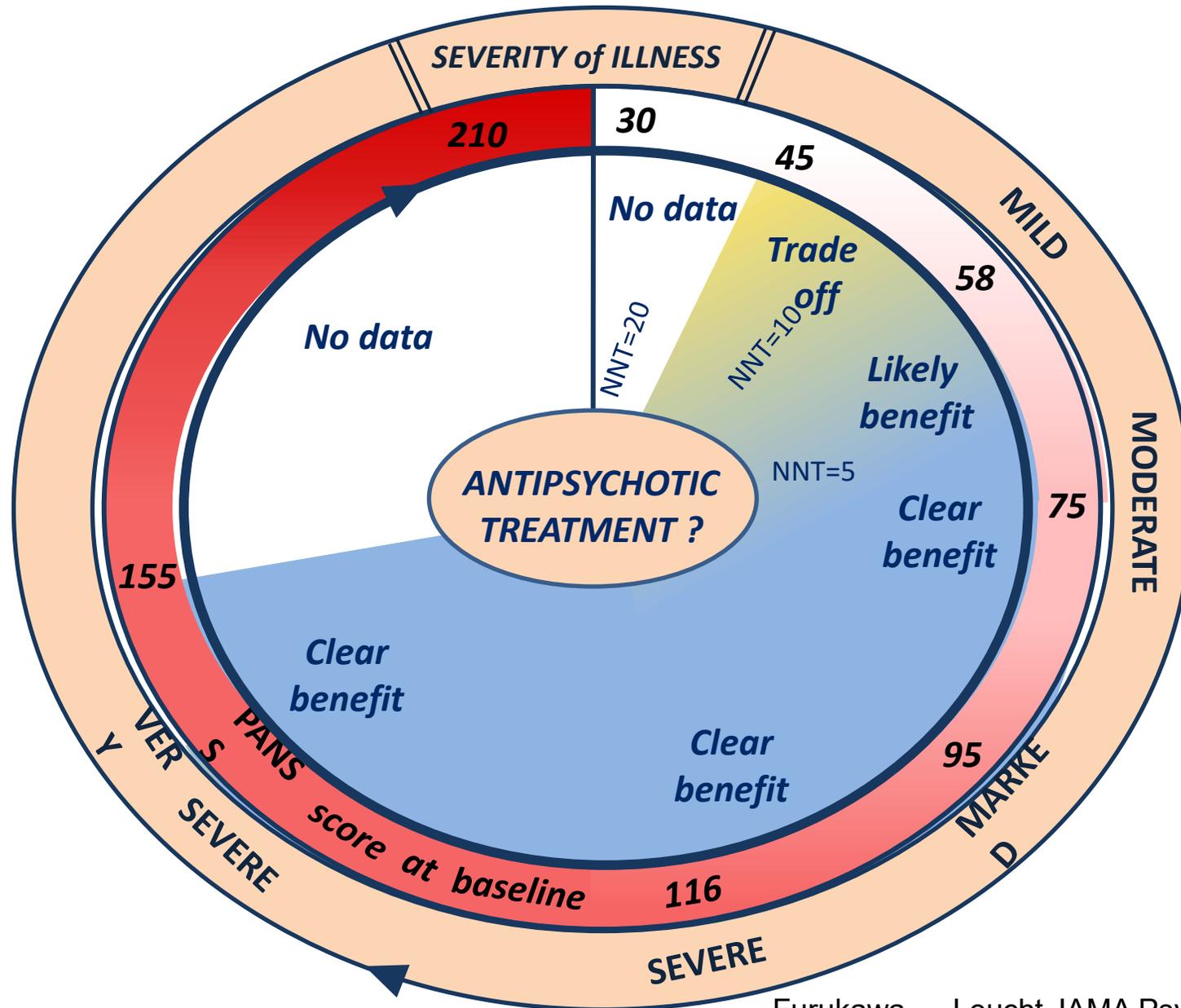
In a re-analysis of > 1000 patients from placebo-controlled olanzapine and risperidone trials, response to antipsychotics was larger in severely ill patients than mildly ill patients

In milder forms the efficacy tolerability balance is worse

Thus confirm the diagnosis well, use lower doses, and more tolerable drugs



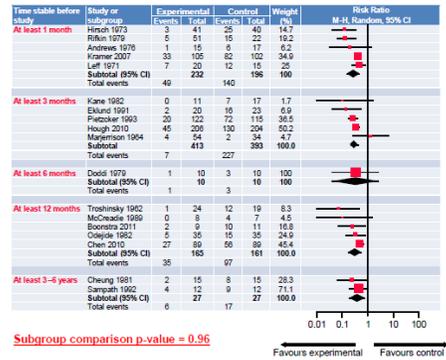
“Antipsychotic clock”



Dose-response meta-analysis

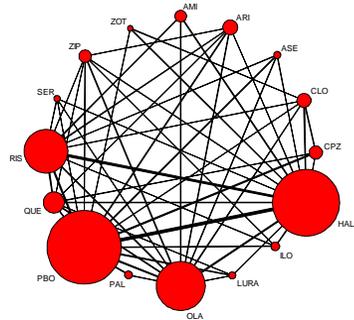
Added value of systematic reviews

Cochrane Reviews Pairwise meta-analysis



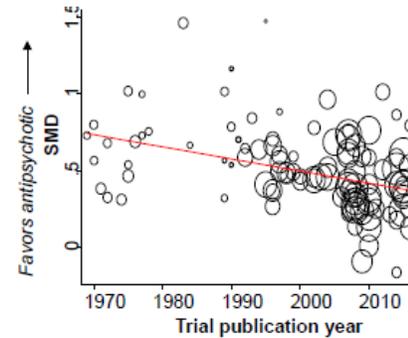
Leucht et al. Lancet 2012,
Cochr Database Syst Rev 2012

Network meta-analysis



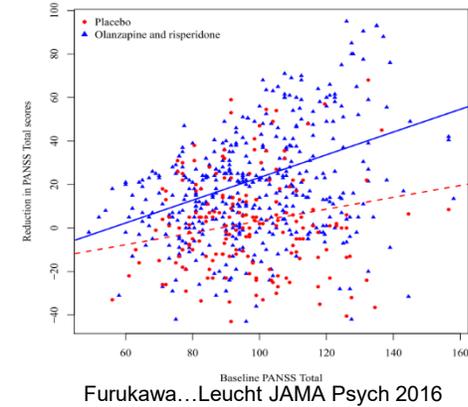
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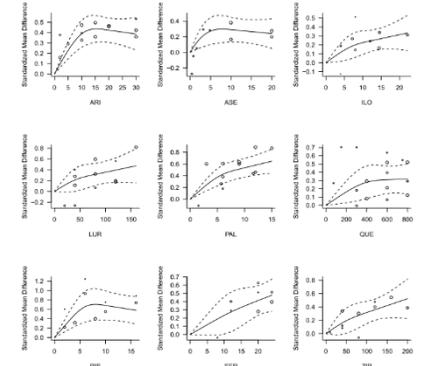
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Individual Patient Data (IPD) Meta-analyses



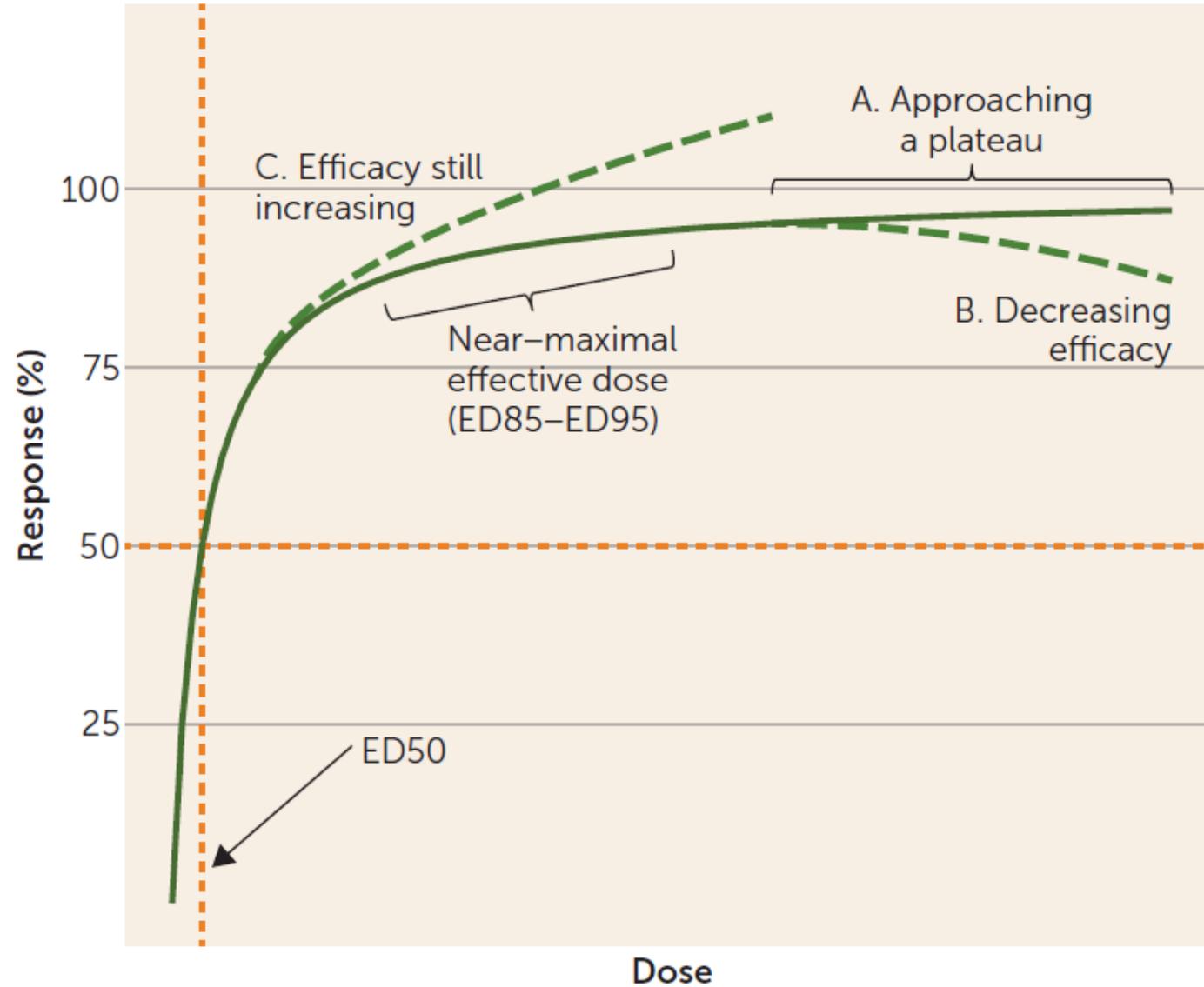
Furukawa...Leucht JAMA Psych 2016

Dose-Response Meta-analysis



Leucht et al. Am J Psych 2020

Schematic dose response curve



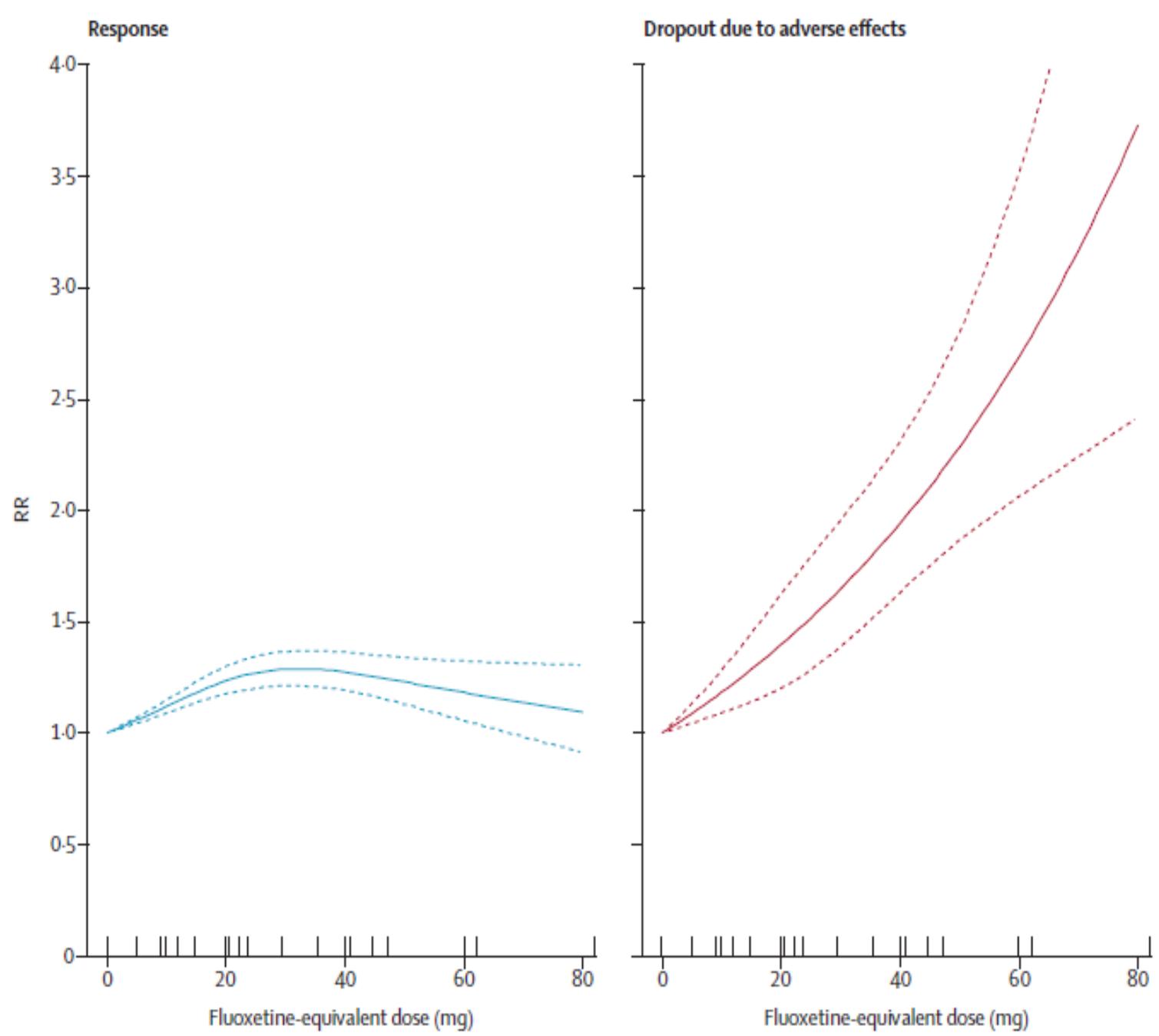
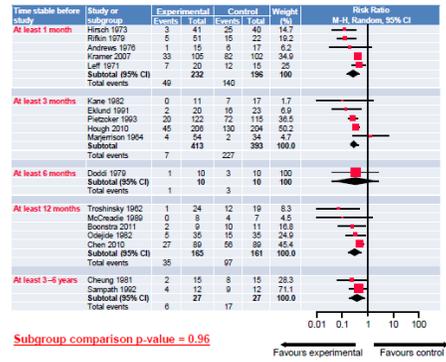


Figure 2: Dose-outcome relationships for selective serotonin reuptake inhibitors (99 treatment groups)

Diagnostic test reviews

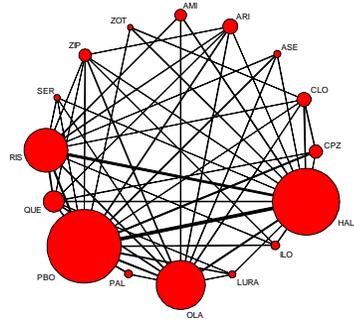
Advanced methods

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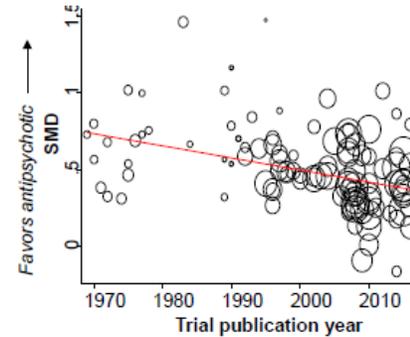
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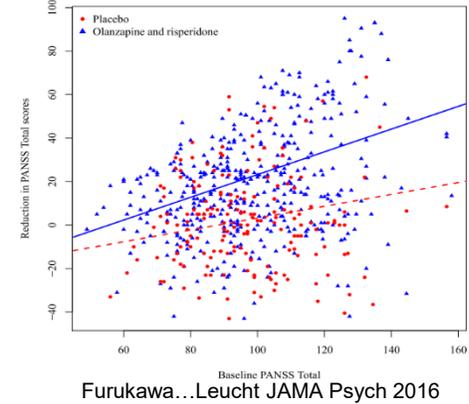
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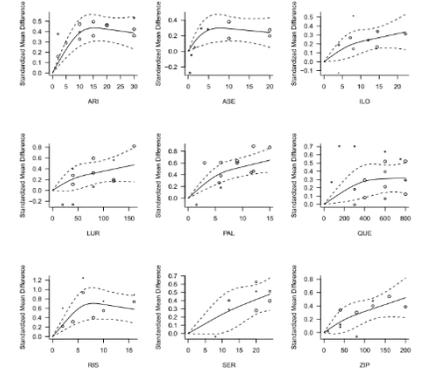
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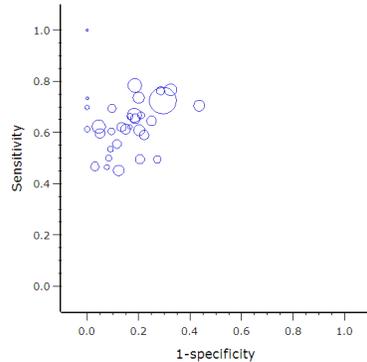
Furukawa...Leucht JAMA Psych 2016

Dose-Response Meta-analysis



Leucht et al. Am J Psych 2020

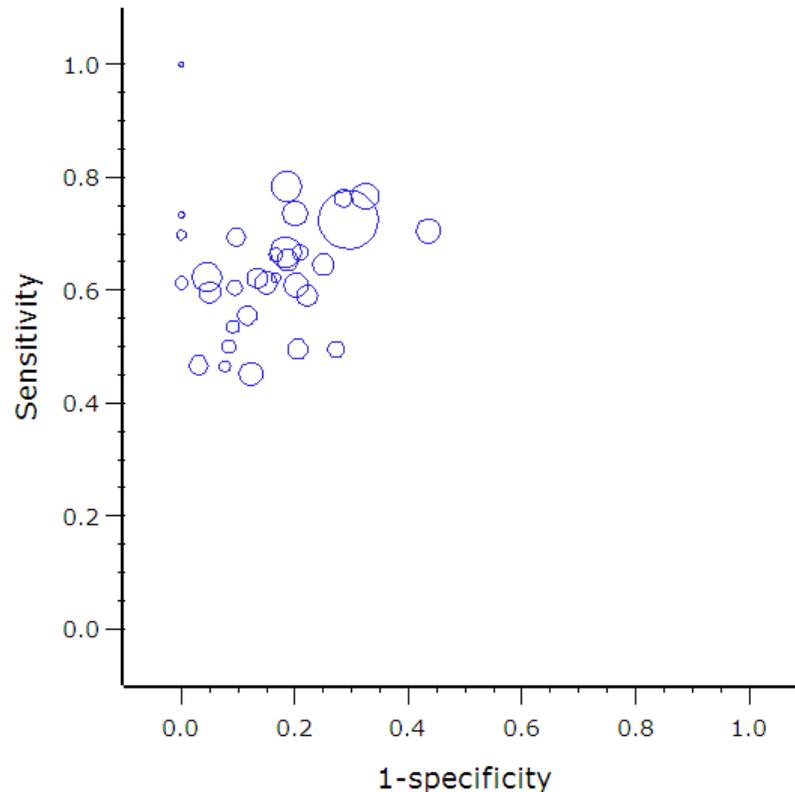
Diagnostic Test Reviews



Samara...Leucht Am J Psych 2015

Diagnostic test review

Meta-analysis of Studies on Early Prediction of Response

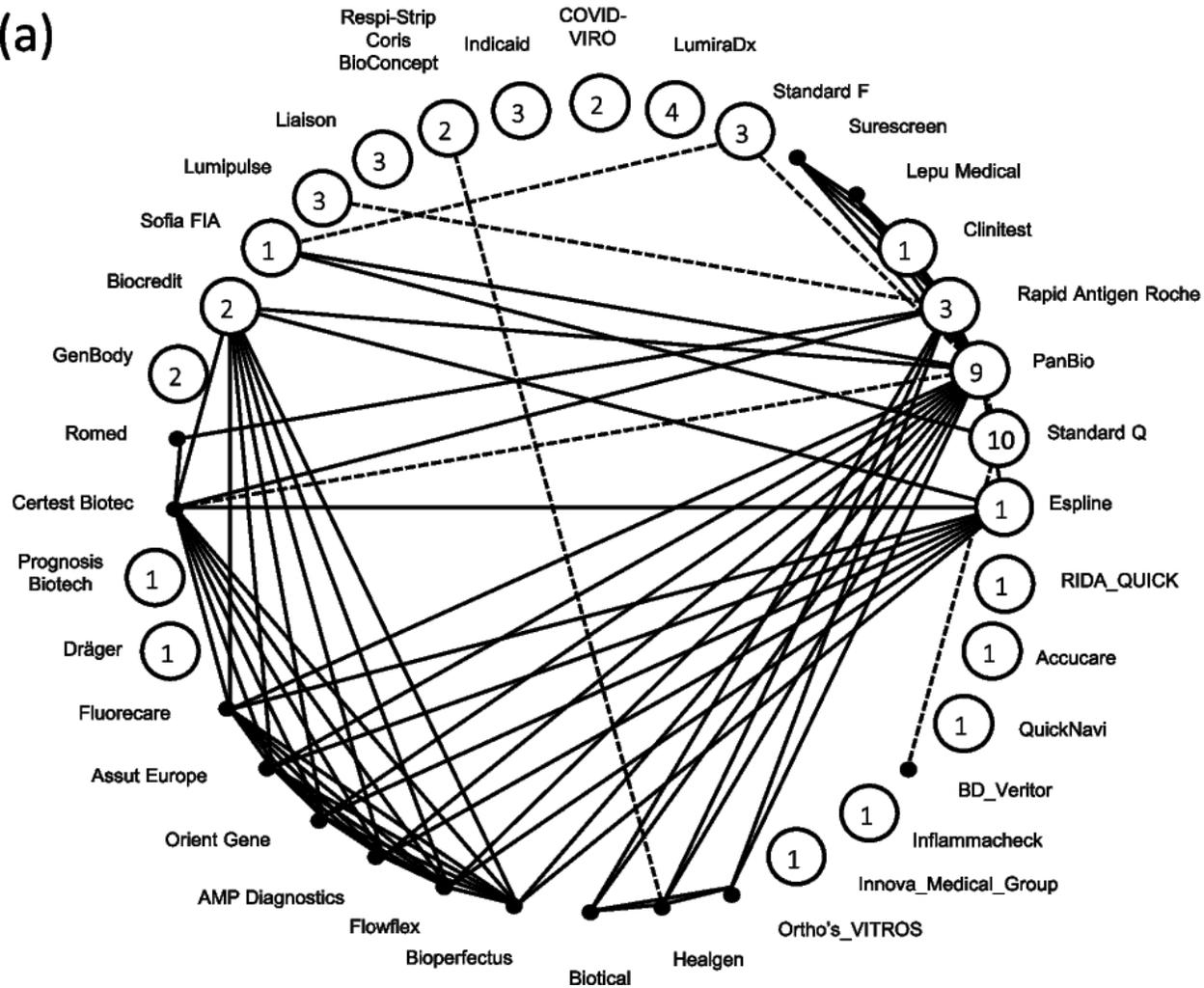


Individual results of 32 trials.
Circle size reflects sample size

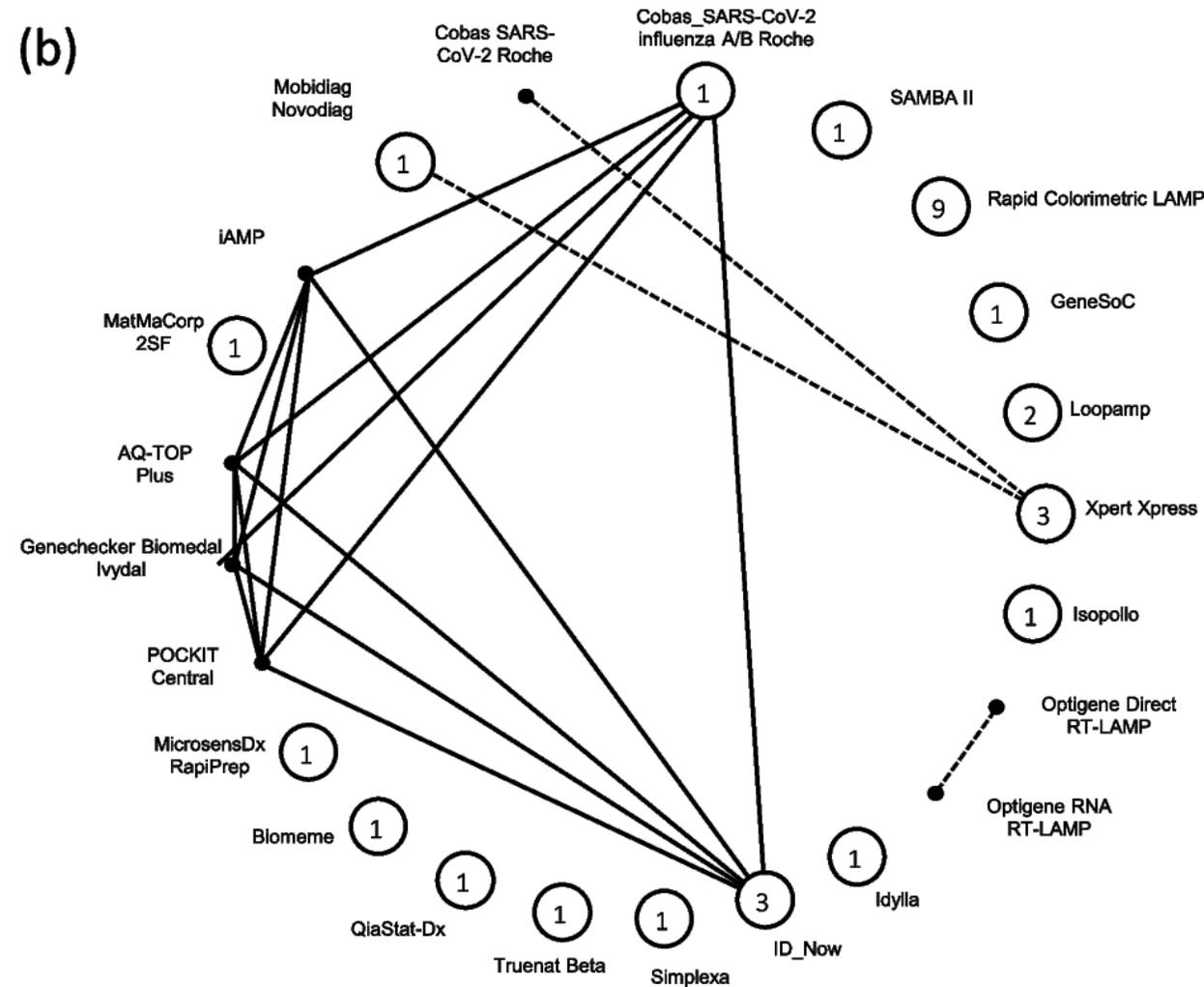
Less than 25% BPRS/PANSS total score reduction at 2 weeks predicted non-response defined as less than 50% BPRS total score reduction at 6 weeks with a **specificity of 86%** in a diagnostic test review of 32 trials.

Diagnostic test network meta-analysis: rapid tests for COVID-19

(a)

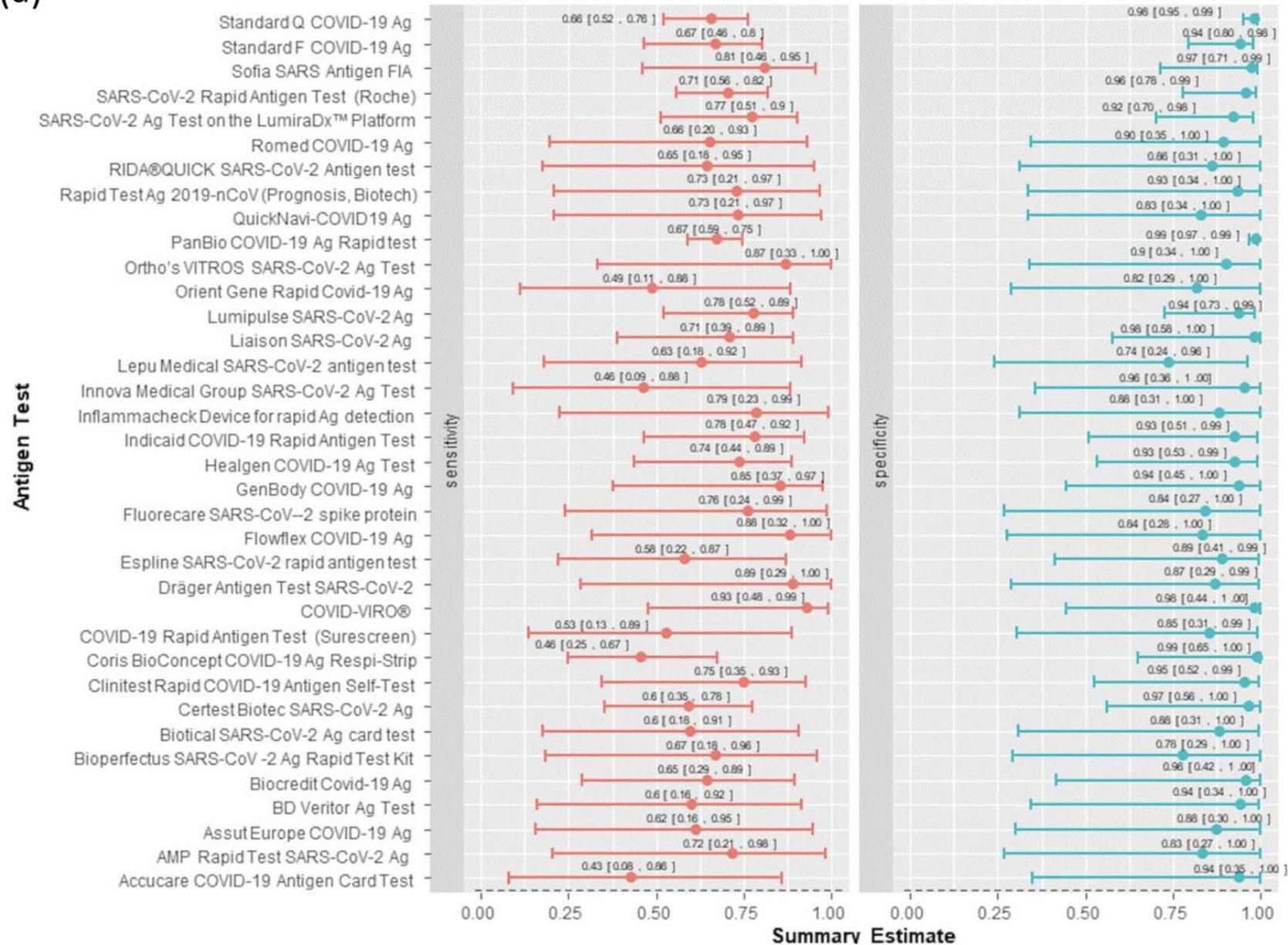


(b)



93 studies relating to 36 rapid antigen tests in 104,961 participants and 23 rapid molecular tests in 10,449 participants

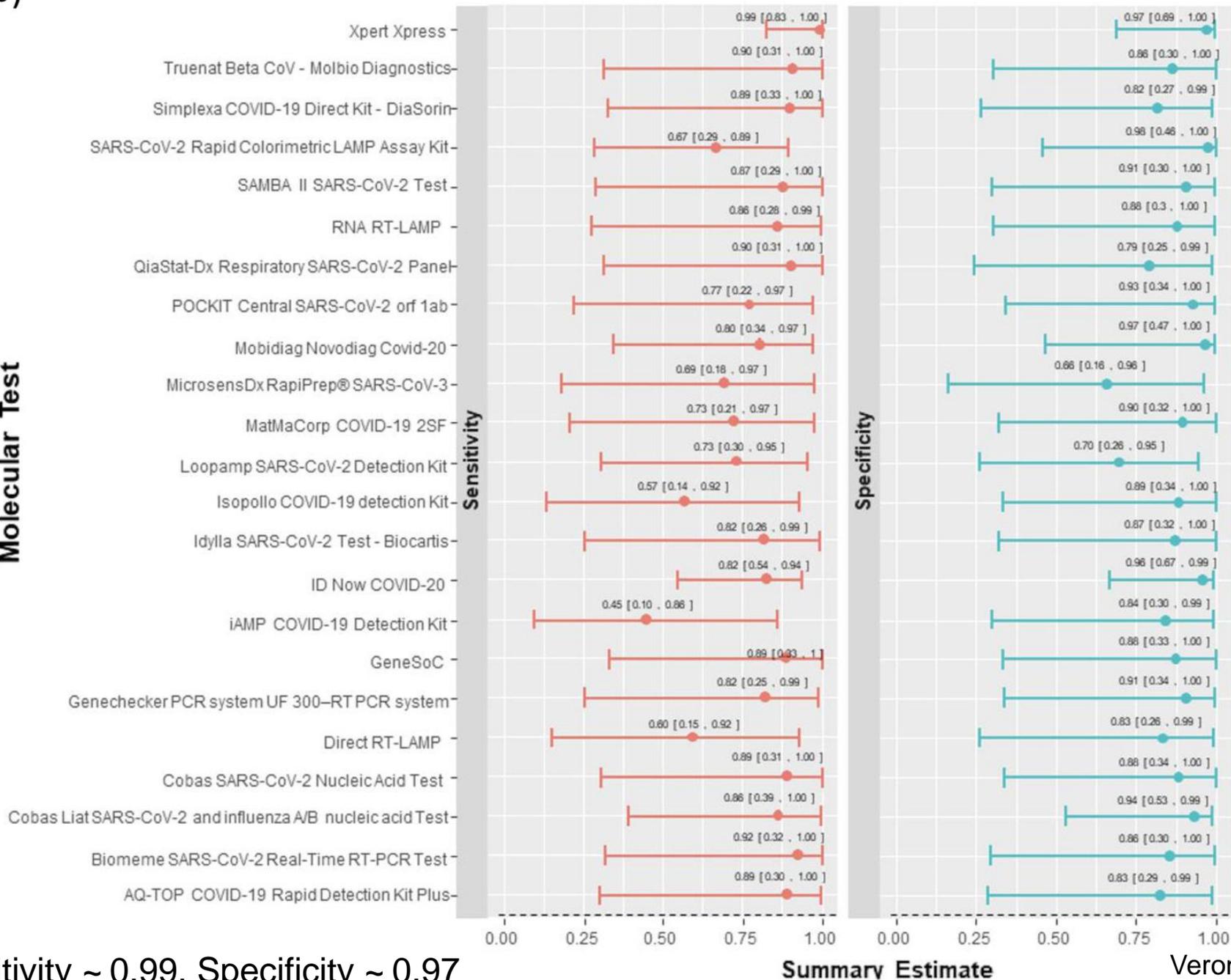
(a)



Antigen-Tests: Sensitivity ~ 0.75, Specificity ~ 0.99

(b)

Molecular Test



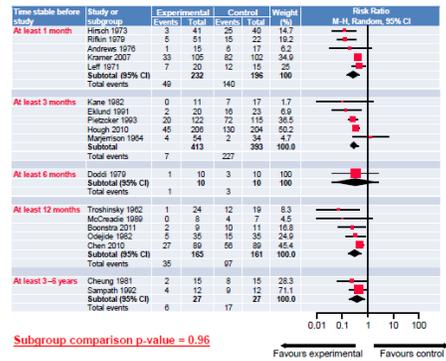
Sensitivity ~ 0.99, Specificity ~ 0.97

Summary Estimate

Overviews of Reviews (Umbrella Reviews)

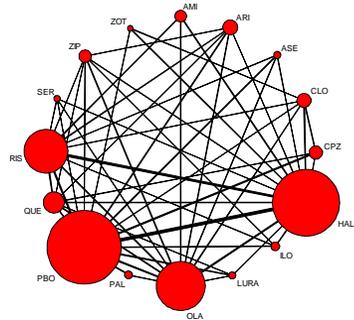
Added value of systematic reviews

Cochrane Reviews Pairwise meta-analysis



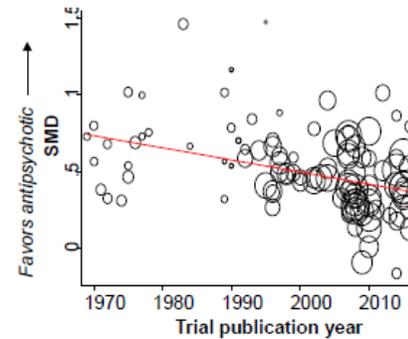
Leucht et al. Lancet 2012,
Cochr Database Syst Rev 2012

Network meta-analysis



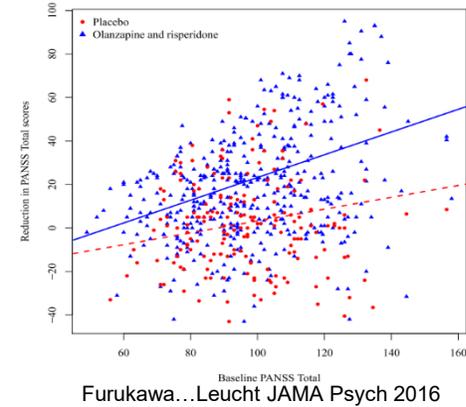
Leucht et al. Lancet 2013,
Huhn...Leucht Lancet 2019

Metaregression



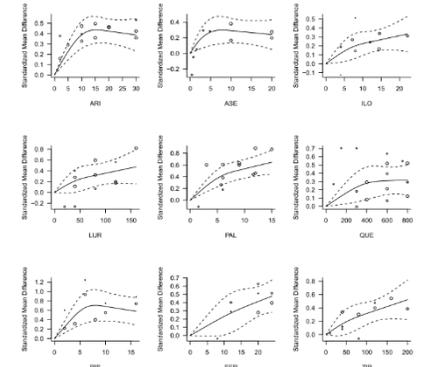
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Individual Patient Data (IPD) Meta-analyses



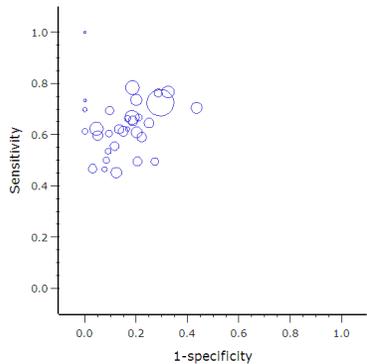
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Dose-Response Meta-analysis



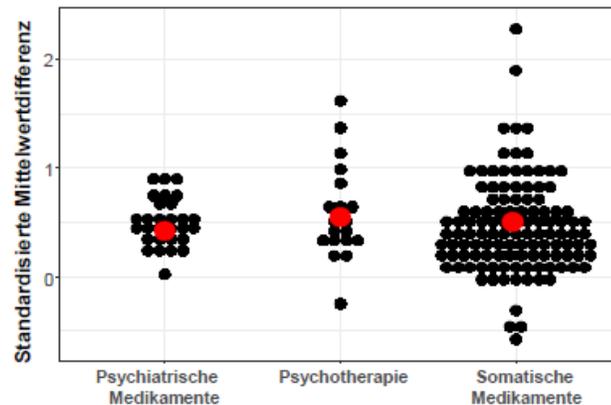
Leucht et al. Am J Psych 2020

Diagnostic Test Reviews



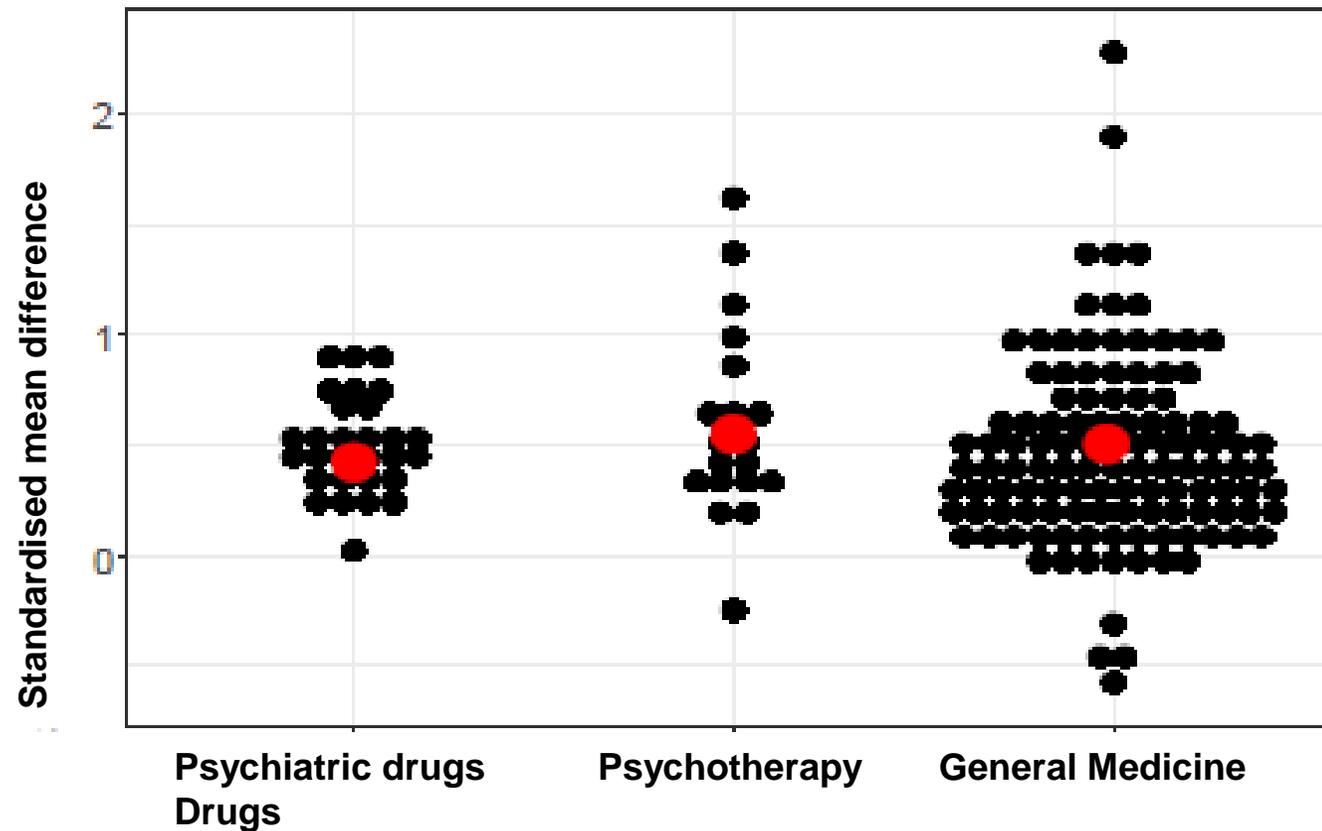
Samara...Leucht Am J Psych 2015

Overviews of Reviews



Leucht et al. Br J Psych 2012,
Huhn...Leucht Leucht JAMA Psych 2016

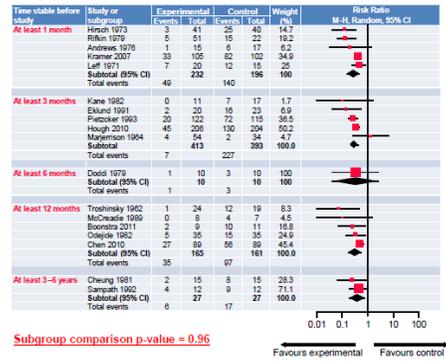
Effect sizes of general medicine and psychiatric drugs and psychotherapy



Systematic reviews on the quality of rating scales

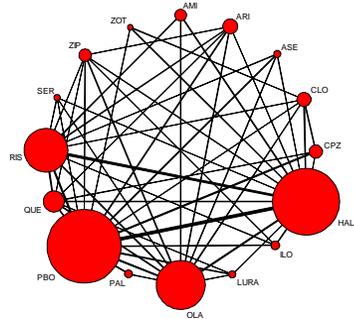
Advanced methods

Cochrane Reviews Pairwise meta-analysis



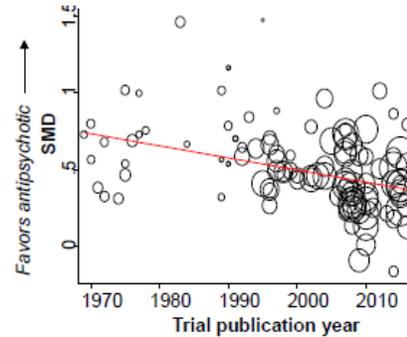
Leucht et al. Lancet 2012,
Cochr Database Syst Rev 2012

Network meta-analysis



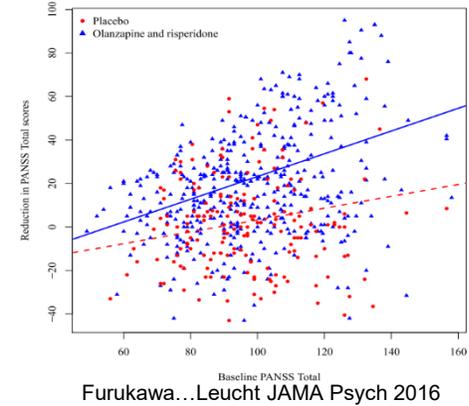
Leucht et al. Lancet 2013,
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Metaregression



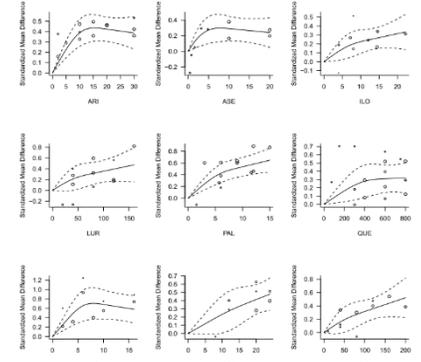
Leucht et al. Am J Psych 2017

Individual Patient Data (IPD) Meta-analyses



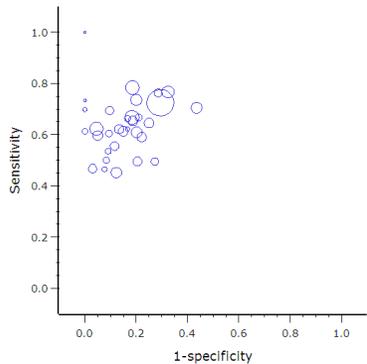
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Dose-Response Meta-analysis



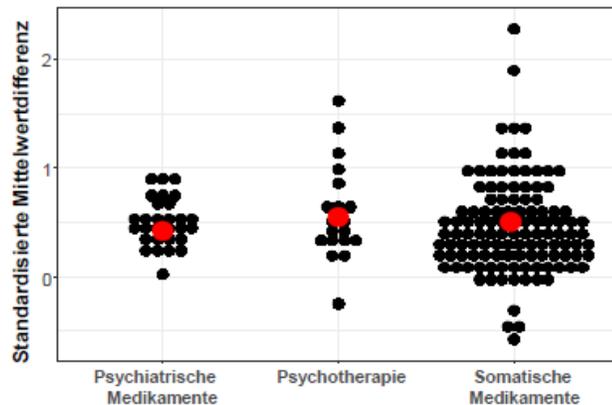
Leucht et al. Am J Psych 2020

Diagnostic Test Reviews



Samara...Leucht Am J Psych 2015

Overviews of Reviews



Leucht et al. Br J Psych 2012,
Huhn...Leucht Leucht JAMA Psych 2016

Systematic Reviews on the Quality of Rating Scales



Weigl...Leucht Schiz Bull 2023

REVIEW ARTICLE OPEN



The Brief negative Symptom Scale (BNSS): a systematic review of measurement properties

Lucia Weigel¹, Sophia Wehr¹, Silvana Galderisi^{1b2}, Armida Mucci^{1b2}, John Davis^{1b3}, Giulia Maria Giordano^{1b2} and Stefan Leucht^{1b3}Clinical Assessment Interview for Negative Symptoms (CAINS)
Review of Measurement PropertiesSophia Wehr^{1,*}, Lucia Weigel¹, John Davis^{2,3}, Silvana Galderisi⁴, Armida Mucci^{4,*}, and Stefan Leucht^{1,*}

Risk of Bias Checklist
Evaluate the reporting quality of the included studies („Very good“, „adequate“, „doubtful“ or „inadequate“)
Box 1. <i>ClinROM development</i>
Box 2. <i>Content validity</i>
Box 3. <i>Structural validity</i>
Box 4. <i>Internal consistency</i>
Box 5. <i>Cross-cultural validity/ Measurement invariance</i>
Box 6. <i>Reliability</i>
Box 7. <i>Measurement error</i>
Box 8. <i>Criterion validity</i>
Box 9. <i>Hypotheses testing for construct validity</i>
Box 10. <i>Responsiveness</i>



Updated criteria for good measurements
Evaluate the quality of the instrument itself by rating each result against criteria of good measurement properties (sufficient (+), insufficient (-), or indeterminate (?)) *
<i>Structural validity</i> : CTT, IRT/Rasch
<i>Internal consistency</i> : Cronbach's alpha
<i>Cross-cultural validity/ Measurement invariance</i> : differences between group factors in multiple group factor analysis, DIF
<i>Reliability</i> : ICC, weighted Kappa
<i>Measurement error</i> : SDC, LoA, MIC
<i>Criterion validity</i> : Correlation with gold standard, AUC
<i>Hypotheses testing for construct validity</i> : accordance with hypothesis
<i>Responsiveness</i> : accordance with hypothesis, AUC



GRADE approach	
Summarize the evidence and grade the quality of the evidence ^o	
Quality of evidence	
High	Risk of bias -1 Serious -2 Very serious -3 Extremely serious
Moderate	Inconsistency -1 Serious -2 Very serious
Low	Imprecision -1 total n=50-100 -2 total n<50
Very low	Indirectness -1 Serious -2 Very serious



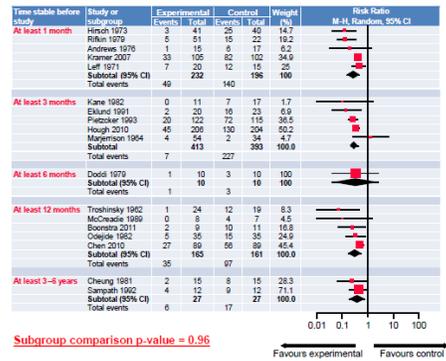
Formulate recommendations	
(A) ClinROMs with evidence for sufficient content validity (any level) AND at least low quality evidence for sufficient internal consistency	<i>can be recommended for use, results can be trusted</i>
(B) ClinROMs categorized not in A or C	<i>have potential to be recommended for use, but require further research to assess the quality</i>
(C) ClinROMs with high quality evidence for an insufficient measurement property	<i>should not be recommended for use</i>

Network IPD meta-analysis

Component network IPD meta-analysis

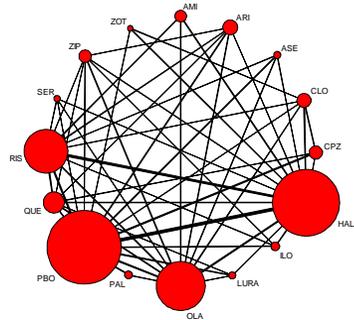
Advanced methods

Cochrane Reviews Pairwise meta-analysis



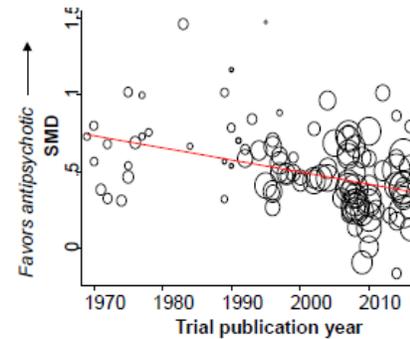
Leucht et al. Lancet 2012,
Cochr Database Syst Rev 2012

Network meta-analysis



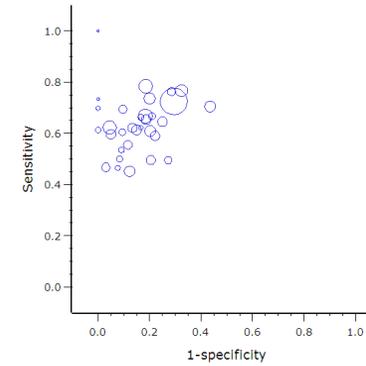
Leucht et al. Lancet 2013,
Huhn...Leucht Lancet 2019

Metaregression



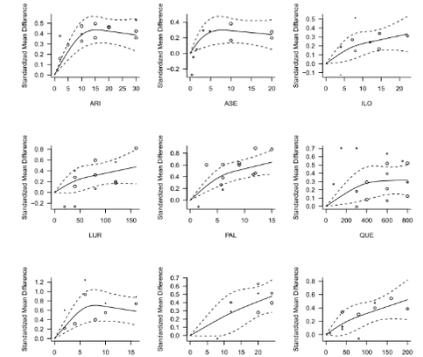
Leucht et al. Am J Psych 2017

Diagnostic Test Reviews



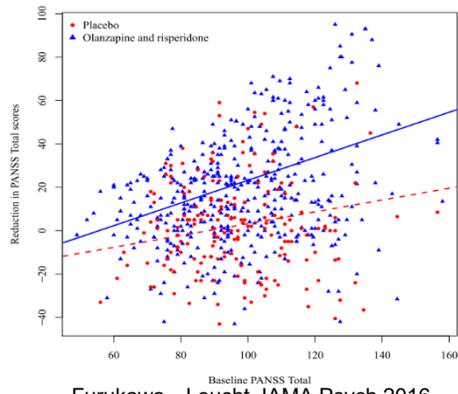
Samara...Leucht Am J Psych 2015

Dose-Response Meta-analysis



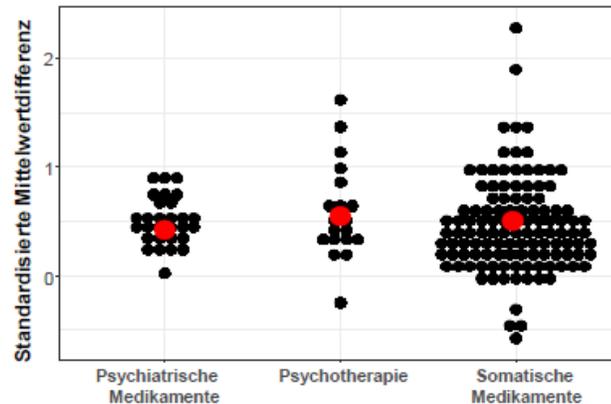
Leucht et al. Am J Psych 2020

Individual Patient Data (IPD) Meta-analyses



Furukawa...Leucht JAMA Psych 2016

Overviews of Reviews



Leucht et al. Br J Psych 2012,
Huhn...Leucht Leucht JAMA Psych 2016

Systematic Reviews of Rating Scales



Weigl...Leucht Schiz Bull 2023

Component IPD Network Meta-analyses

	Depression severity (IMD of PHQ-9 scores, median (95% CrI))
Age	0.19 (-0.09 to 0.47)
Baseline depression, PHQ-9 scores	2.59 (2.32 to 2.85)
Gender*	-0.03 (-0.28 to 0.18)
Relationship†	-0.12 (-0.33 to 0.12)
Waiting component	0.42 (-0.75 to 1.53)
Non-specific treatment effects	-1.41 (-2.52 to -0.30)
Psychoeducation about depression	0.02 (-0.86 to 0.93)
Cognitive restructuring	0.30 (-0.87 to 1.41)
Behavioural activation	-1.81 (-2.90 to -0.80)
Interpersonal skills training	-0.54 (-1.59 to 0.52)
Problem solving	-0.64 (-1.41 to 0.09)
Relaxation	1.20 (0.17 to 2.27)
Third-wave components	-0.53 (-1.55 to 0.49)
Behaviour therapy for insomnia	-1.82 (-3.92 to 0.26)
Relapse prevention	0.35 (-0.69 to 1.32)
Homework required	0.31 (-0.69 to 1.35)
Initial face-to-face contact	0.85 (-1.80 to 3.41)
Automated encouragement to proceed with CBT	-0.26 (-1.13 to 0.60)
Human encouragement to proceed with CBT	-0.29 (-1.17 to 0.58)
Therapeutic guidance for CBT	0.01 (-0.88 to 0.89)

Furukawa...Lancet Psych 2021

Component IPD Network Meta-analysis

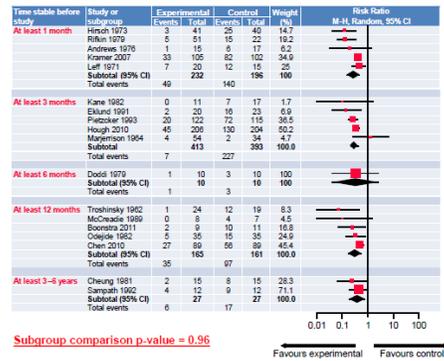
Which components of CBT are effective for depression?

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Cumulative network meta-analysis

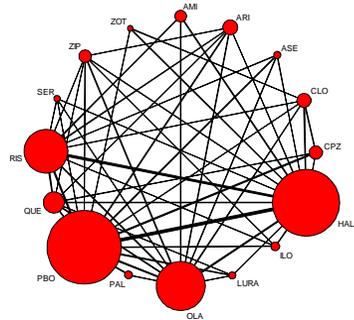
Advanced methods

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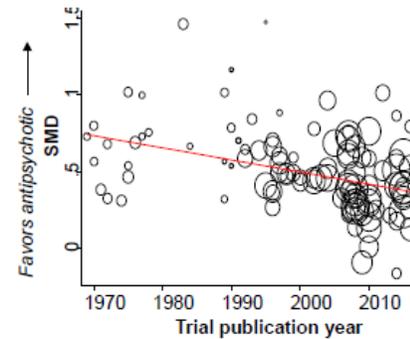
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Network meta-analysis



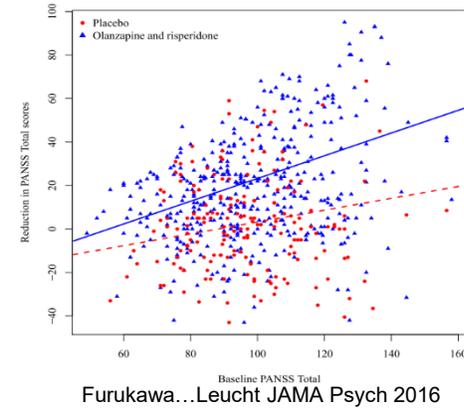
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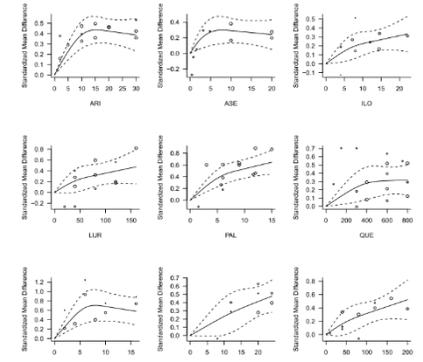
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Individual Patient Data (IPD) Meta-analyses



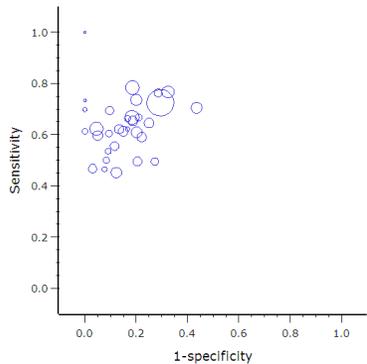
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Dose-Response Meta-analysis



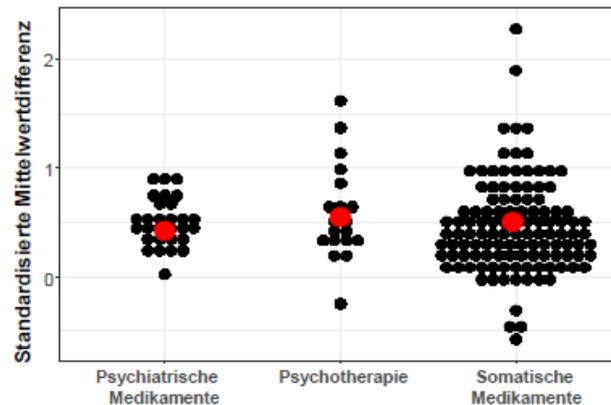
Leucht et al. Am J Psych 2020

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Samara...Leucht Am J Psych 2015

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Huhn...Leucht Leucht JAMA Psych 2016

Systematische Reviews über Skalen



Weigl...Leucht Schiz Bull 2023

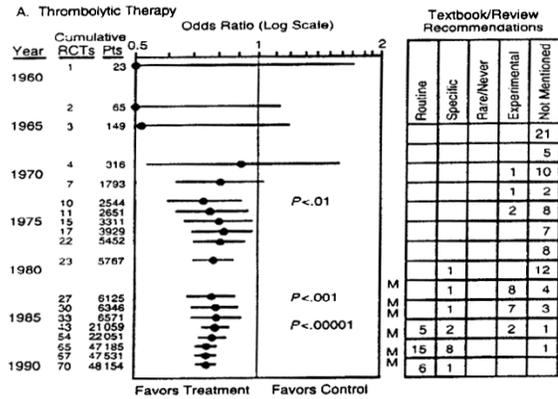
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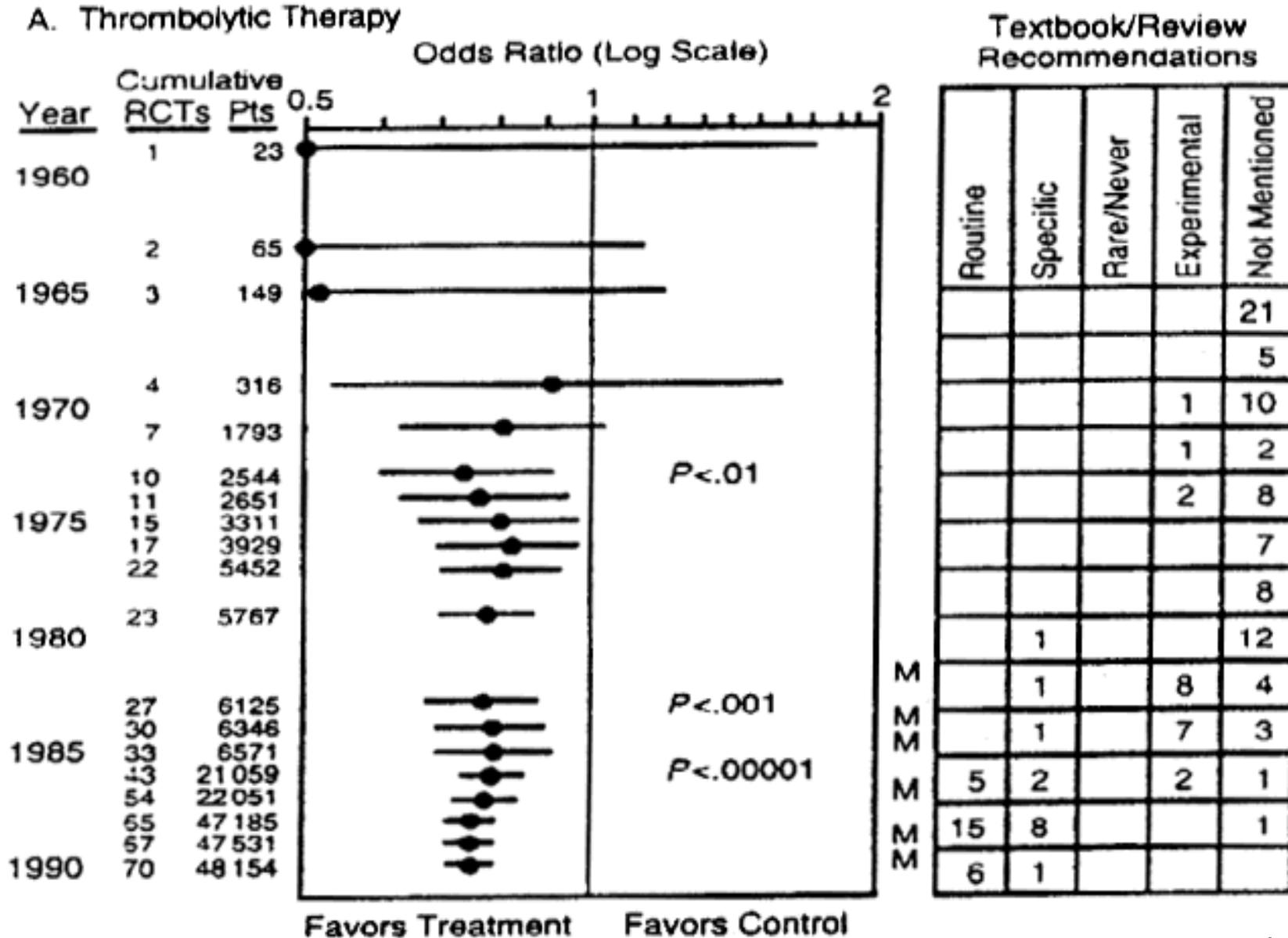
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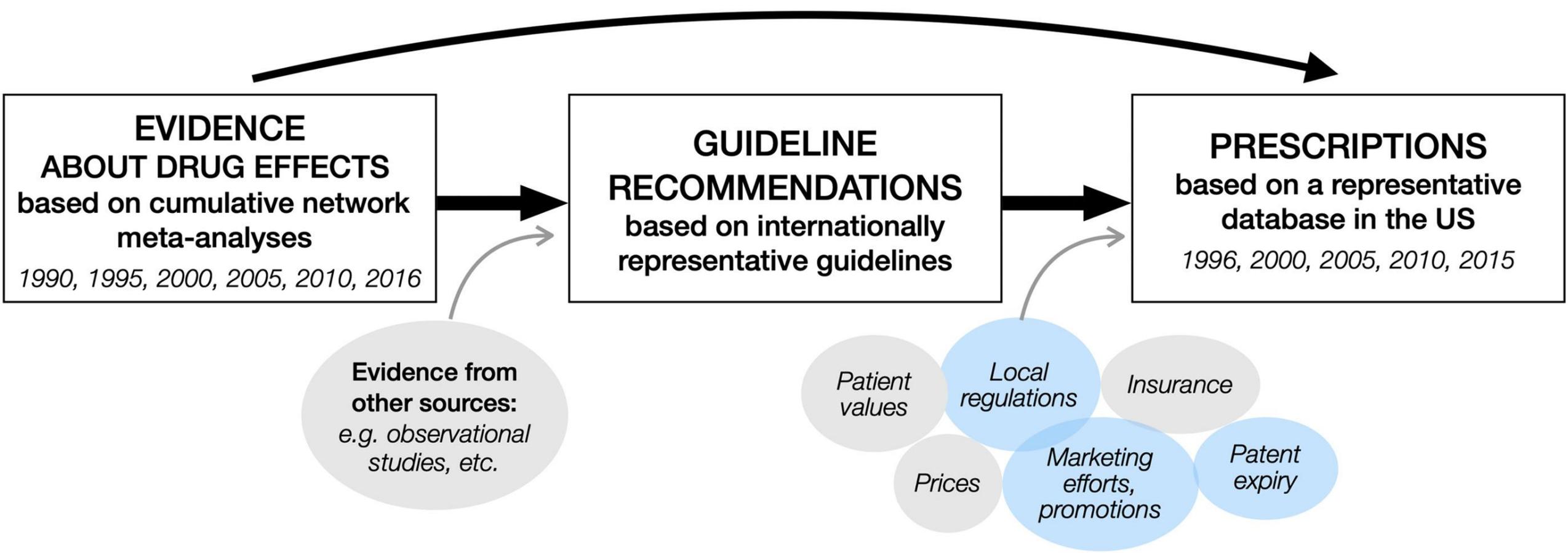
Advanced network meta-analytic methods

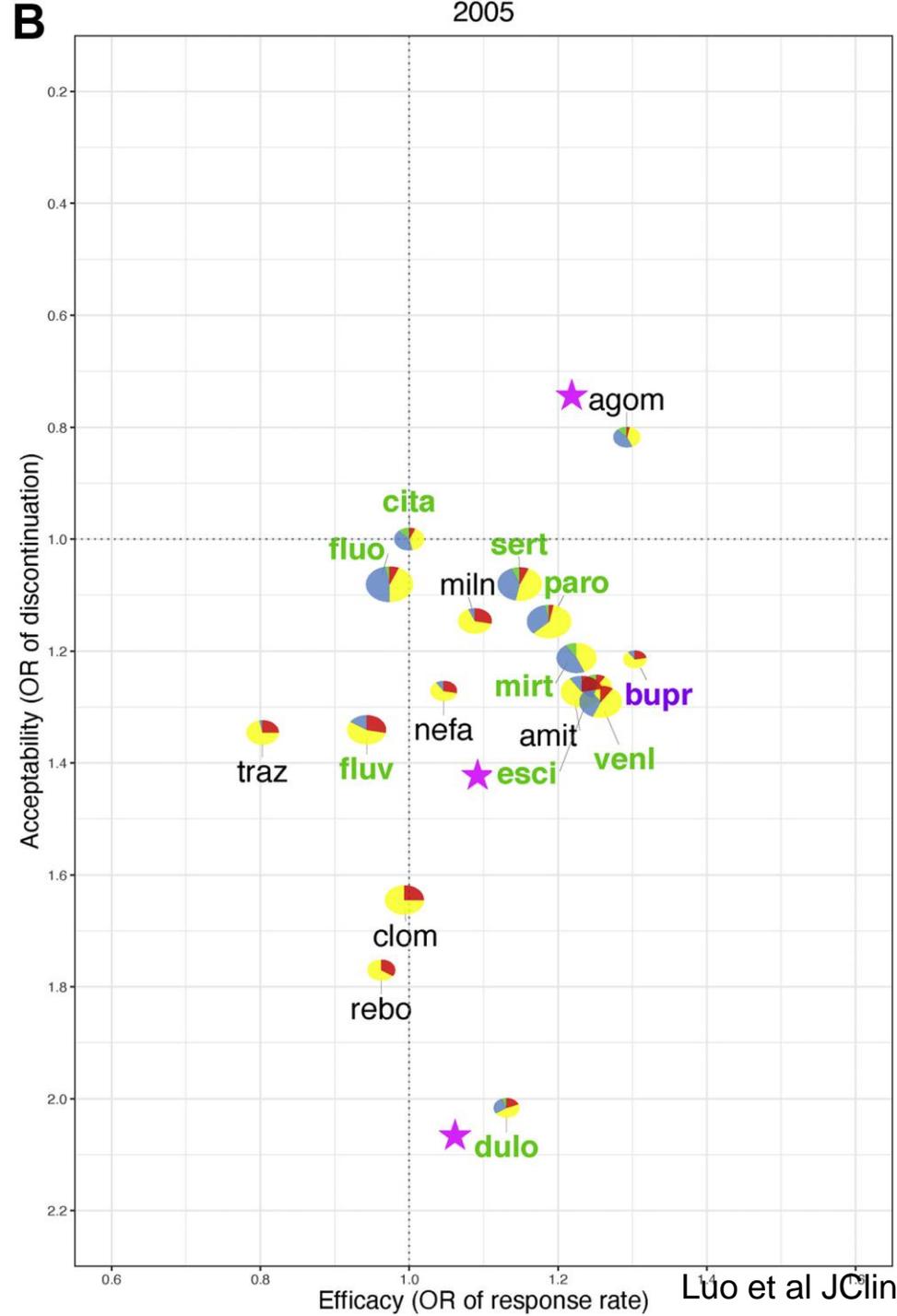
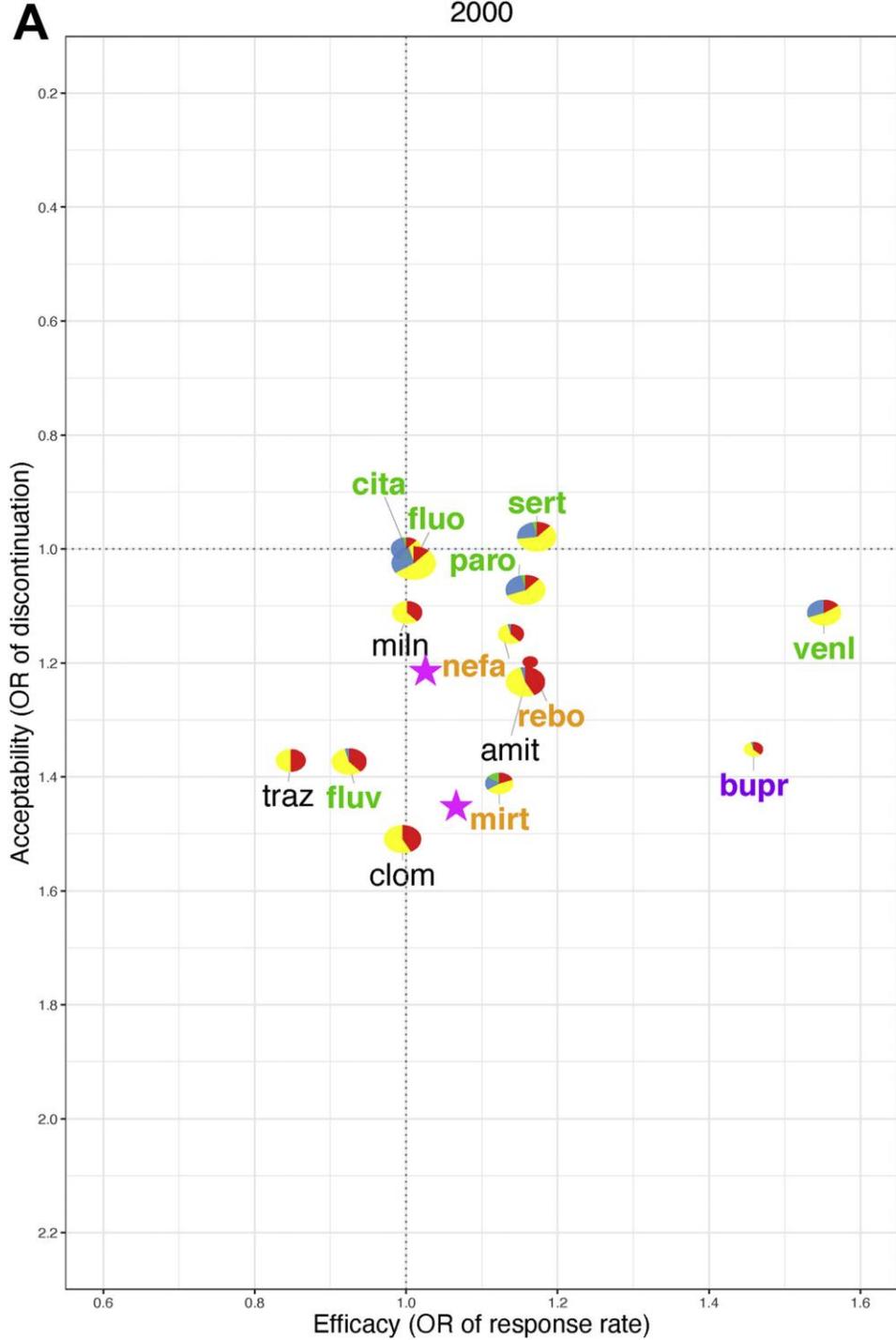
Cumulative meta-analysis

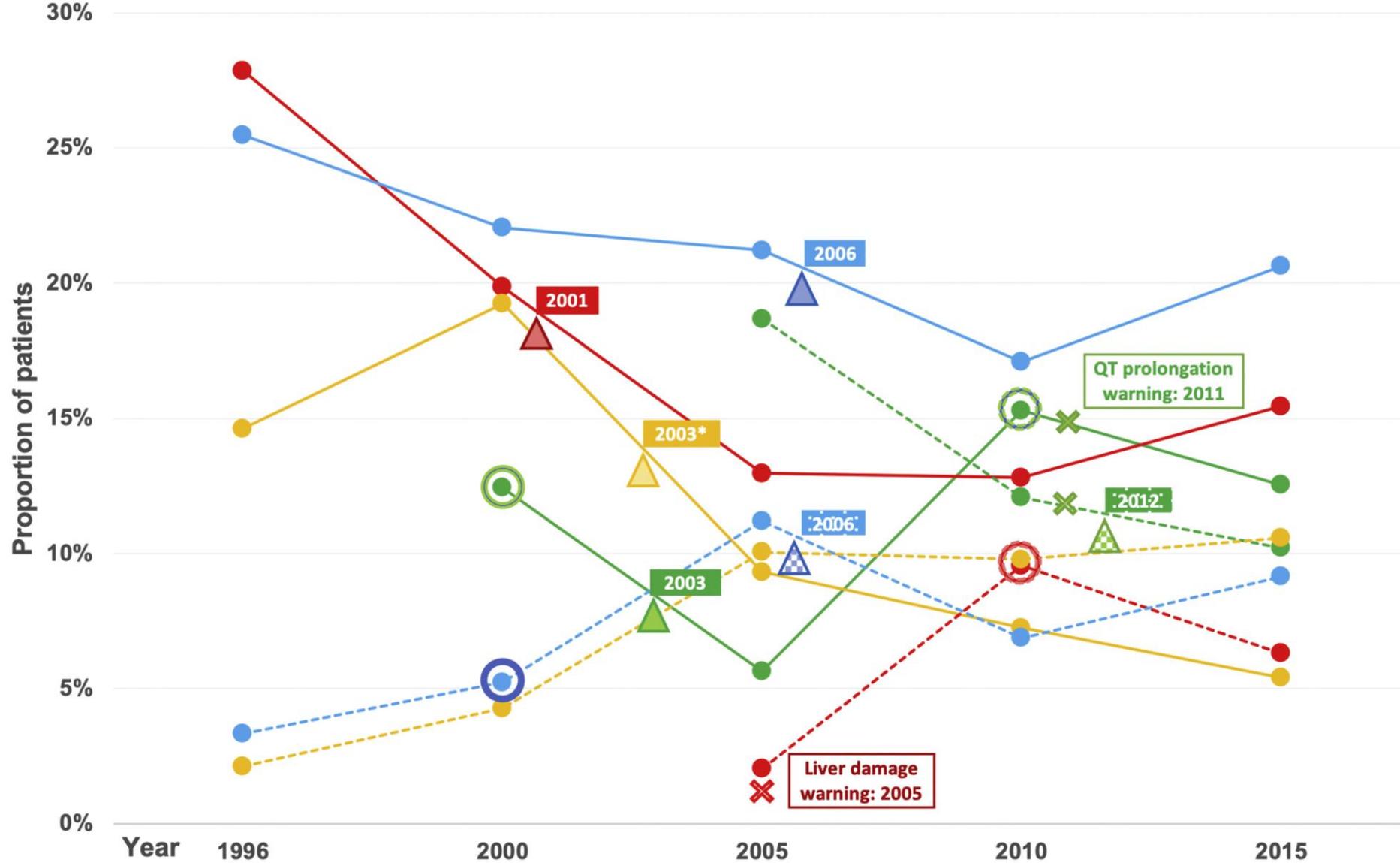


Cumulative meta-analysis







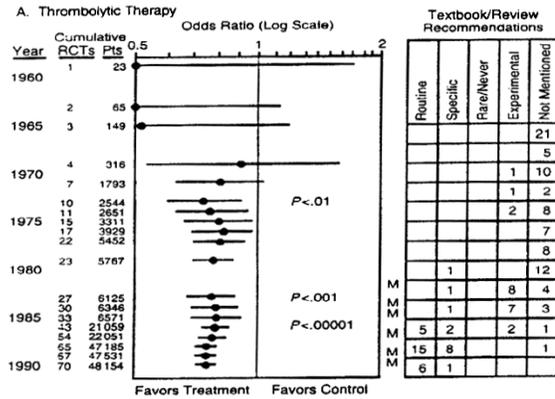


- citalopram
- fluoxetine
- sertraline
- paroxetine
- - -●- - - escitalopram
- - -●- - - duloxetine
- - -●- - - venlafaxine
- - -●- - - bupropion

Living meta-analysis

Advanced network meta-analytic methods

Cumulative meta-analysis



Living meta-analysis





80 volunteers experienced in meta-analysis
do study selection and data extraction on
the web

<https://mhccovid.ispm.unibe.ch>



MHCOVID

a continuously updated meta-ecological study of the effects of the COVID-19 pandemic on mental health



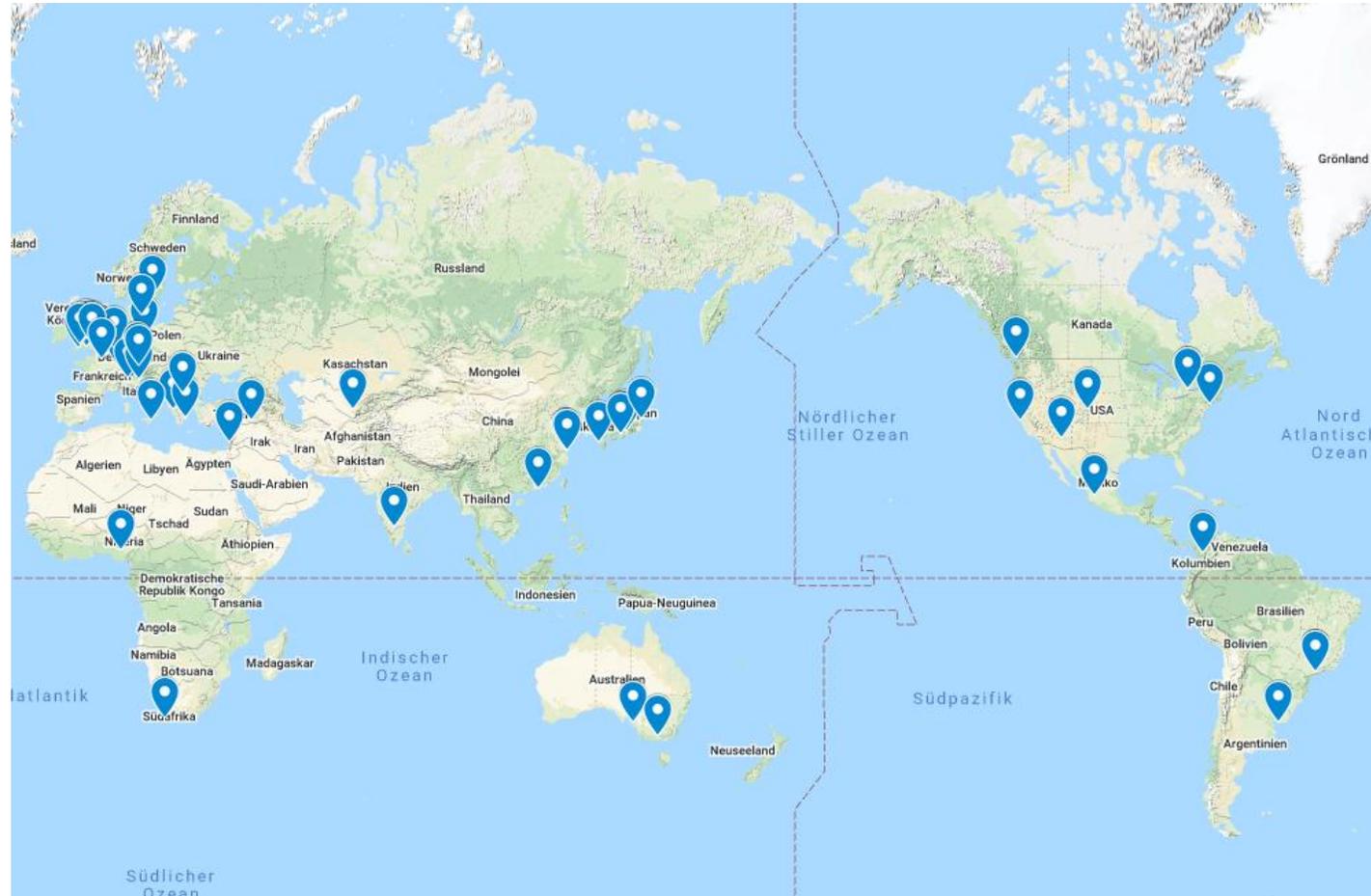
Swiss National
Science Foundation

MHCOVID

- ❖ living systematic review
- ❖ Associations between worsening of mental health during the COVID-19 pandemic with
 - extent of pandemic
 - stringency measures

Crowdsourcing

100 volunteers experienced in systematic reviews from all continents



Website

Mental Health COVID

MHCOVID is a living online systematic review of scientific evidence about changes in the prevalence of mental health issues due to the COVID-19 pandemic and containment measures.

We take a **global view**, and seek to determine how the extent of containment measures are associated with mental health issues (including violent behaviour, and alcohol and substance abuse) in the general population, as well as various sub-populations. Our project makes use of **crowdsourcing** techniques to increase the quantity of evidence we can include in our analyses, and our results are continuously updated as more evidence becomes available.

43,389 papers screened

3,404 papers included

165 papers extracted



Who we are

The MHCOVID team consists of **9 researchers**, and is advised by a Steering Committee of **12 international experts**. We're assisted in our task by a crowd of over **70 people** from **18 countries** that provide their valuable time for the good of others!

[View details »](#)



Our aim

We seek to provide an innovative, reliable exploration of large-scale evidence about changes in the prevalence of mental health issues resulting from the COVID-19 pandemic and its containment measures.

[View details »](#)



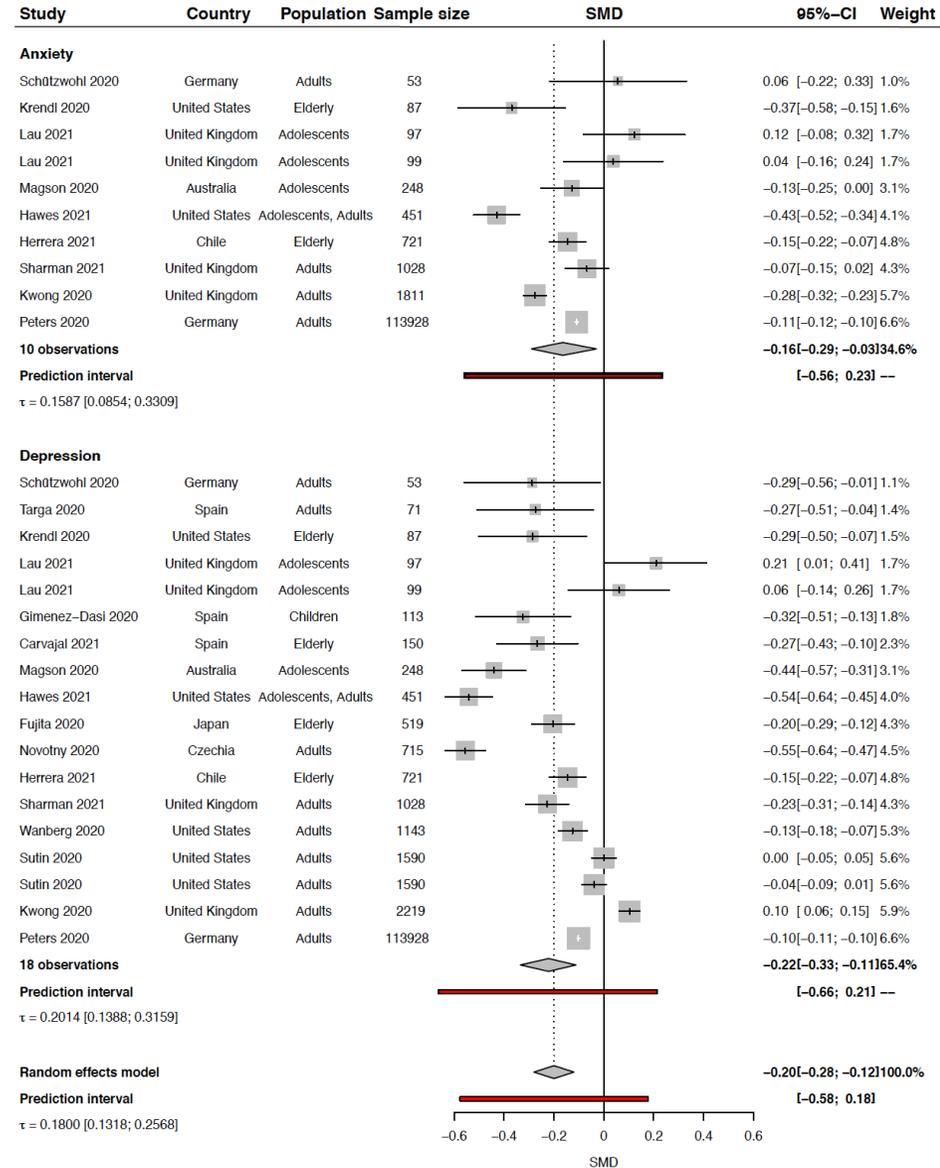
Want to help?

If you'd like to get involved in the project, we'd like to hear from you! We're always looking for more volunteers to join the crowd and help advance the project.

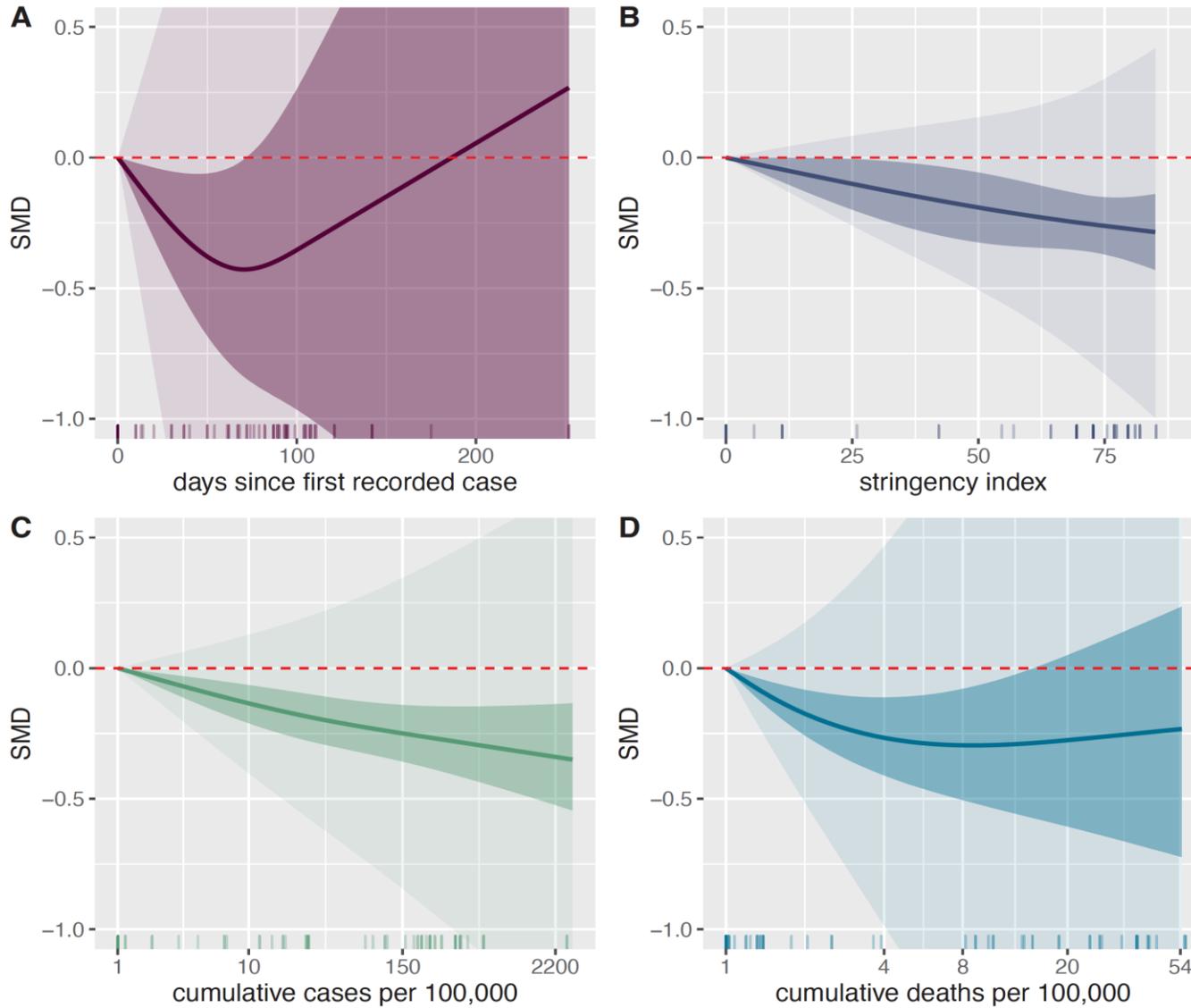
[View details »](#)



MHCOVID Anxiety and Depression

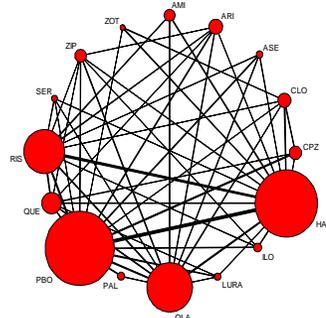


MHCOVID Association with COVID severity and stringency of containment measures



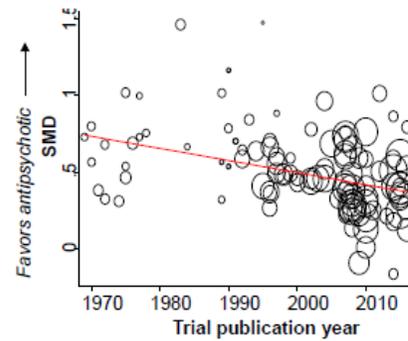
Advanced meta-analytic methods

Network meta-analysis



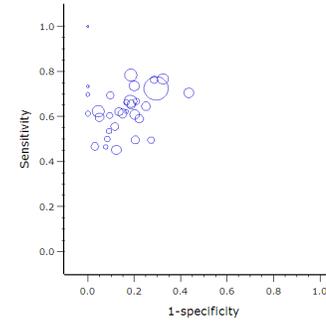
Leucht et al. Lancet 2013, Huhn...Leucht Lancet 2019

Metaregression



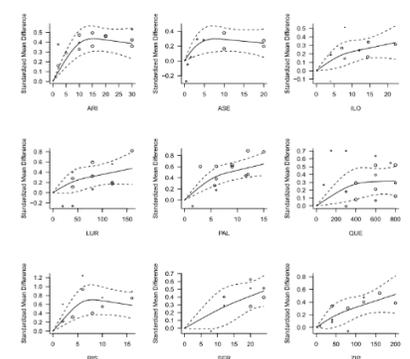
Leucht et al. Am J Psych 2017

Diagnostic Test Reviews



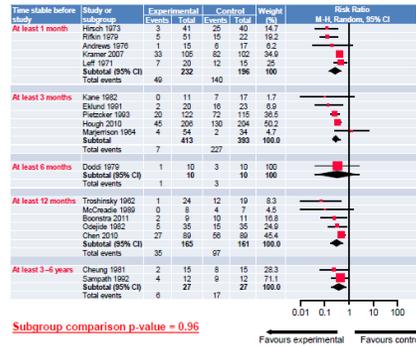
Samara...Leucht Am J Psych 2015

Dose-Response Meta-analysis



Leucht et al. Am J Psych 2020

Cochrane Reviews Pairwise meta-analysis



Leucht et al. Lancet 2012, Cochr Database Syst Rev 2012

Systematic Reviews



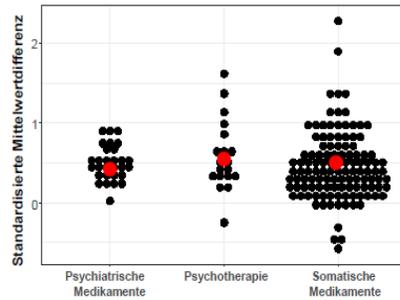
Weigl...Leucht Schiz Bull 2023

Component IPD Network Meta-analyses

	Depression severity (MD of PHQ-9 scores, median [95% CI])
Age	0.02 (-0.02 to 0.47)
Baseline depression, PHQ-9 scores	2.59 (2.32 to 2.85)
Gender*	-0.03 (-0.28 to 0.18)
Relationship†	-0.12 (-0.13 to 0.12)
Waiting component	0.42 (0.29 to 0.53)
Non-specific treatment effects	-3.41 (-3.22 to -4.30)
Psychoeducation about depression	0.02 (-0.86 to 0.93)
Cognitive restructuring	0.30 (-0.87 to 1.41)
Behavioral activation	0.81 (0.29 to 0.99)
Interpersonal skills training	-1.54 (-1.53 to 0.52)
Problem solving	-0.64 (-1.42 to 0.09)
Relaxation	3.20 (0.17 to 2.27)
Third-wave components	-0.51 (-1.55 to 0.49)
Behavior therapy for insomnia	-2.82 (-3.92 to 0.26)
Risk prevention	0.25 (-0.60 to 0.23)
Homework required	0.31 (-0.69 to 0.32)
Initial face-to-face contact	0.85 (-1.89 to 1.41)
Automated encouragement to proceed with CBT	-0.26 (-1.12 to 0.60)
Human encouragement to proceed with CBT	-0.29 (-1.17 to 0.58)
Therapeutic guidance for CBT	0.01 (-0.88 to 0.89)

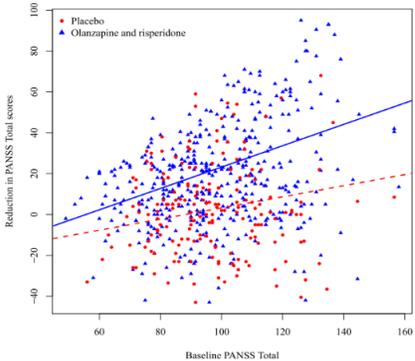
Furukawa...Lancet Pych 2021

Overviews of Reviews



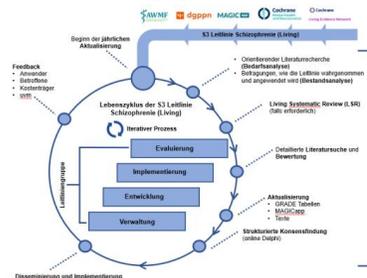
Leucht et al. Br J Psych 2012, Huhn...Leucht Leucht JAMA Psych 2016

Individual Patient Data (IPD) Meta-analyses

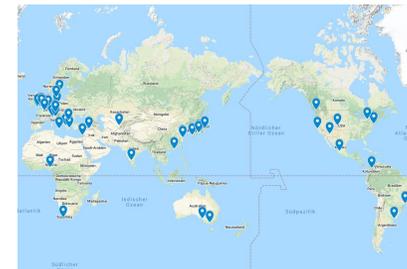


Furukawa...Leucht JAMA Psych 2016

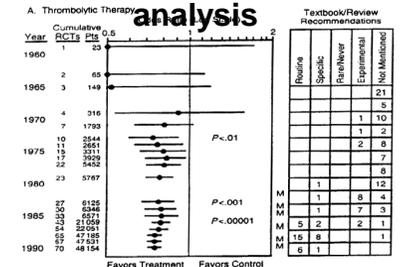
Living guidelines



Living meta-analysis



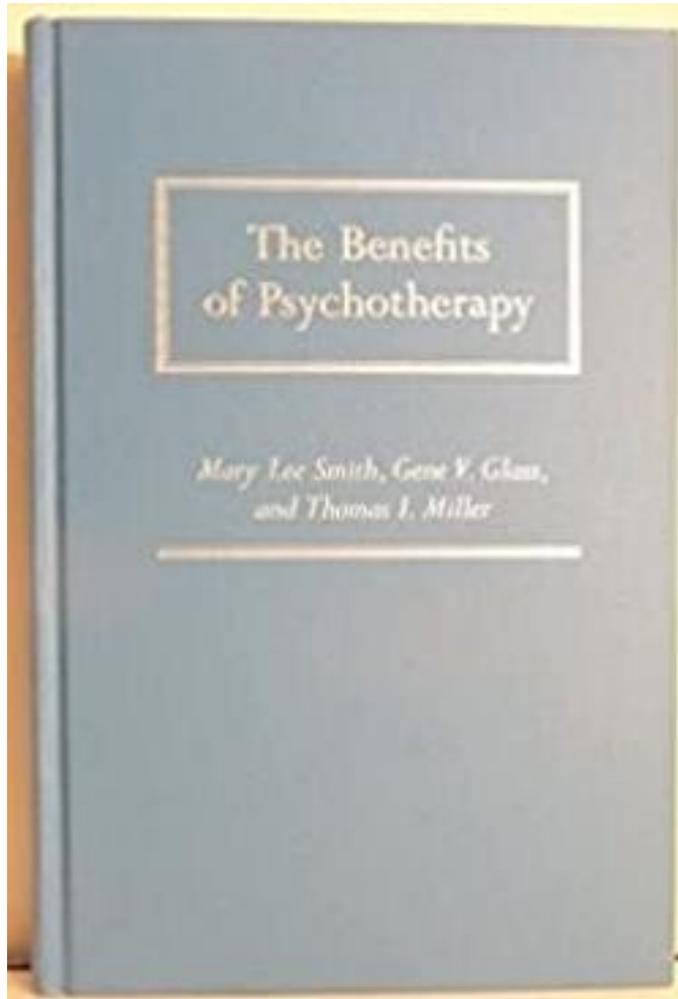
Cumulative meta-analysis



Limitations of Meta-analyses

- The „apples and oranges problem“ - heterogeneity, different study quality etc.

Gene Glass, coined the term meta-analysis



Limitations of Meta-analyses

- The „apples and oranges problem“ - heterogeneity, different study quality etc.
- In meta-analysis there are many judgement calls
- The original studies are frequently so poorly reported that meta-analytic procedures are not possible
- Publication bias

Question

What is publication bias?

1. The department heads are first authors and not the PhD students who do the work
2. Systematic mistakes (=bias) in a publication
3. Studies with negative results end up in the file drawer
4. Studies are published in different pieces

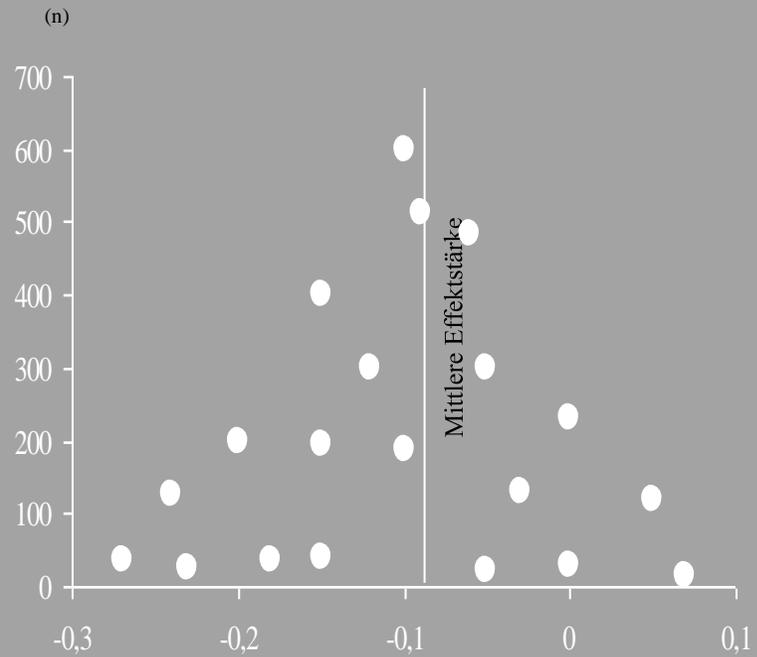
Publication Bias

- Is probably the greatest problem of evidence based medicine – **EVIDENCE BIASED MEDICINE** (Melander et al. 2004)
- Studies without significant results are considered less interesting by journals and thereby have a reduced likelihood of getting published
- Pharmaceutical companies are not interested in publishing studies with results that were unfavourable for their product.
- The situation improved in the early 2000s when major journals made it a requirement that all studies must be registered, e.g. on clinicaltrials.gov, because otherwise they will not be published

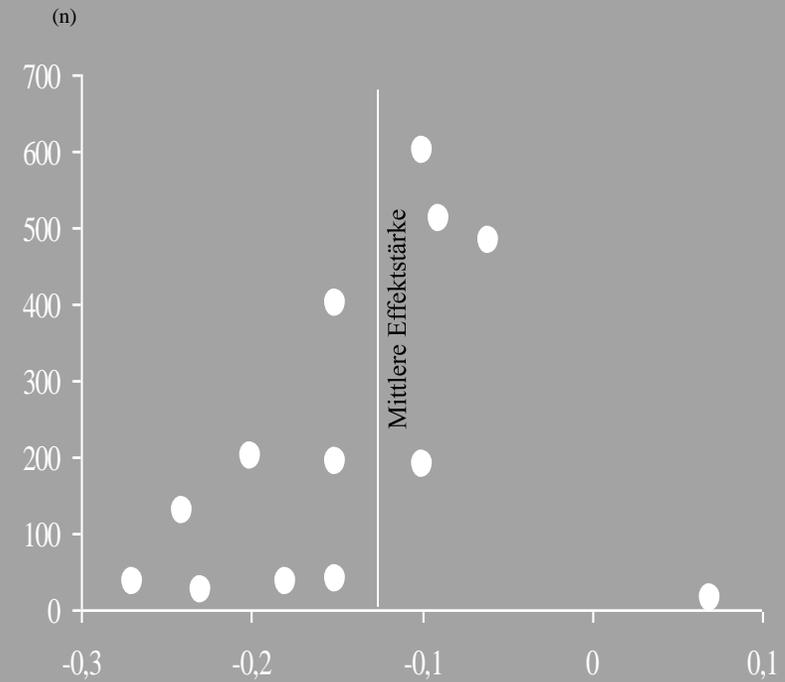
Funnel plot

Method to identify publication bias

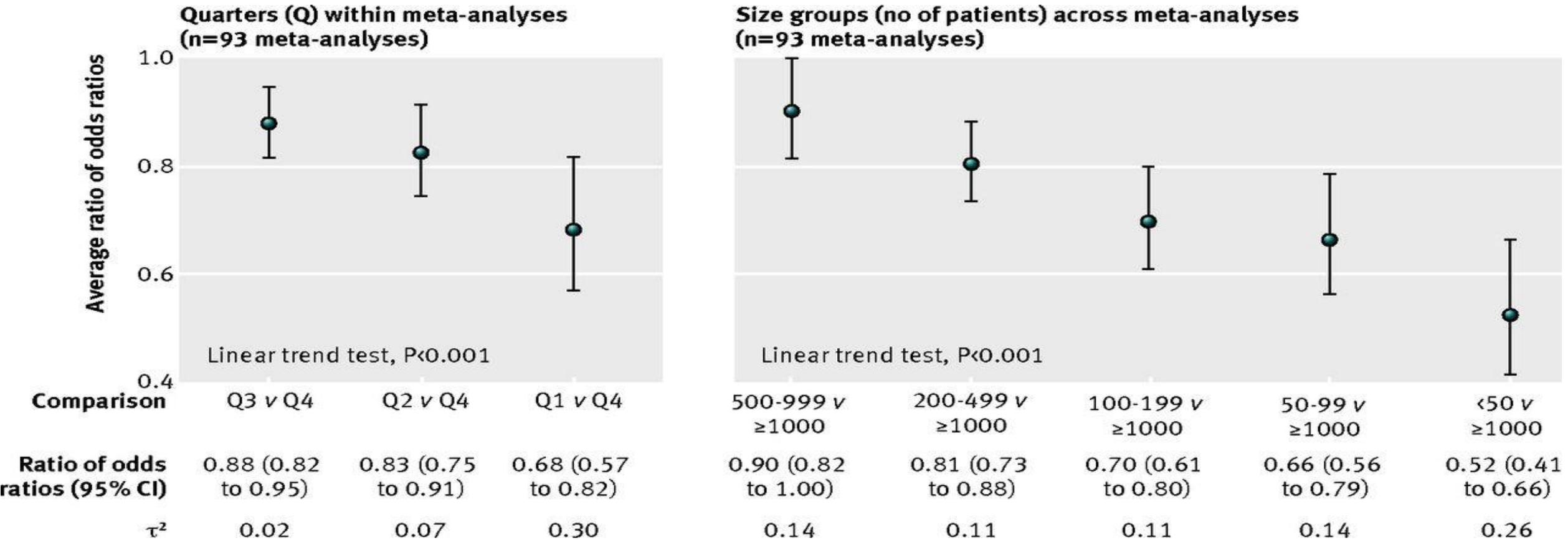
„Funnel-plot“ without publication bias



„Funnel-plot“ showing possible publication bias



Small trials have higher effect sizes



Where to go / Software

- Cochrane Collaboration “RevMan” – very solid, good training, does not have meta-regression, and not the specific forms except overviews and diagnostic test reviews
- Comprehensive Meta-analysis – very user friendly, includes meta-regression, not the specific forms
- STATA
- R various packages – most comprehensive, you find a package for everything including Bayesian approaches, dose-response etc

GUIDELINE



- Acute phase
- Special situations
- Treatment-resistant patients
- Maintenance phase
- Side effects

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CO-CREATE

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TOOLS

SmPC SUMMARY OF PRODUCT CHARACTERISTICS (A-C)

This document provides a concise summary of the key characteristics of an antipsychotic product, drawing information from regulatory bodies such as the FDA, EMA, and HPRA. This file includes the following antipsychotics: Amisulpride, Aripiprazole, Asenapine, Brexpiprazole, Cariprazine, Chlorpromazine,

WHO DAILY-DEFINED-DOSES (DDD)

WHO Defined Daily Dose (DDD) Lookup – search the official WHO ATC/DDD Index to find standardized DDDs for antipsychotics, antidepressants, and other medicines.

REFERENCE

antidepressants, mood stabilizers,

TOOLS

**SUMMARY OF PRODUCT CHARACTERISTICS (A-C)**

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**SUMMARY OF PRODUCT CHARACTERISTICS (D-Z)**

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**DRUGBANK INTERACTION CHECKER**

Professional database tool for checking potential interactions between medications with comprehensive pharmaceutical information.

**DRUGS.COM INTERACTION CHECKER**

Comprehensive medication interaction checker allowing users to check for potential drug-drug and drug-food interactions.

**SHARED-DECISION-MAKING ASSISTANT (SDMA)**

A Shared-Decision-Making Assistant for schizophrenia treatment that compares antipsychotic medications by efficacy and side effects (weight gain, movement disorders, etc.) to support collaborative treatment decisions.

**PSYMATIK**

Evidence-based psychiatry tools offering an algorithmic schizophrenia guideline (INTEGRATE), antipsychotic and antidepressant treatment optimizers to weigh side effects, and switching guides; delivers personalised treatment recommendations (free sign-up required).

**ANTIPSYCHOTICS DOSE CALCULATOR (EXCEL FILE)**

An Excel file for converting antipsychotic doses can be downloaded from the linked page.

**META CONVERT (AUTOMATED COMPUTATIONS OF EFFECT SIZES)**

A tool for medication conversion calculations and dosage equivalencies.

**WHO DAILY-DEFINED-DOSES (DDD)**

WHO Defined Daily Dose (DDD) Lookup – search the official WHO ATC/DDD Index to find standardized DDDs for antipsychotics, antidepressants, and other medicines.

**SWITCHRX**

Online psychotropic switching tool for clinicians: select the current and target antidepressant or antipsychotic to generate suggested cross-taper/titration schedules, with clinical tips, pharmacokinetic notes, and precautions; also supports transitions from monotherapy to combination regimens; registration required.

**SERIOUS MENTAL ILLNESS ADVISER**

SMI Adviser (APA) – a clinical support system for serious mental illness offering free accredited education, evidence-based resources, and on-demand clinician-to-clinician consultations; access requires login (free account).

**SERIOUS MENTAL ILLNESS ADVISER - LONG-ACTING INJECTABLE ANTIPSYCHOTICS**

Clinician's Guide to Preparing and Administering Long-Acting Injectable Antipsychotics – on-demand APA/SMI Adviser course that teaches clinicians how to discuss LAIs with patients, prepare/handle required supplies, identify IM/SC landmarks, and administer injections step-by-step

**PSYCHOEDUCATION FOR SCHIZOPHRENIA (BY JOSEF BÄUML, IRENE BIGHELLI, AND STEFAN LEUCHT)**

Comprehensive educational resource by Josef Bäuml, Irene Bighelli, and Stefan Leucht providing essential information for patients and caregivers. Download available as PowerPoint slides.

**METACOGNITIVE TRAINING (MCT) OPEN SOURCE**

Metacognitive Training (MCT) Open Source – download editable developer versions of MCT for Psychosis and MCT+ (PowerPoint & Word) to adapt slides (e.g., culture-specific exercises/phrasing) for non-commercial use.

**RELAPSE RISK VS. ANTIPSYCHOTIC DOSE**

Interactive tool showing dose-dependent relapse risk based on risperidone equivalents (Leucht 2021). Convert other antipsychotics using the included converter.

**AGNP THERAPEUTIC DRUG MONITORING GUIDELINES (THERAPEUTIC PLASMA REFERENCE RANGES)**

Consolidated tables of therapeutic plasma reference ranges for 154 psychotropic and neurologic drugs (antipsychotics, antidepressants, mood stabilizers, antiepileptics), with methods to define lower/upper limits, dose-related reference ranges (C/D) to flag PK anomalies, and laboratory alert levels; recommends interpreting trough steady-state concentrations and lists when TDM is indicated.

**ANTICHOLINERGIC BURDEN CALCULATOR (ABC)**

Anticholinergic Cognitive Burden (ACB) Calculator – enter a medication list to sum per-drug anticholinergic scores (0–3) and automatically flag high risk at totals ≥ 3 (linked to confusion, falls, and higher mortality); includes a searchable Medicines Scorecard and practical options to reduce burden.

**FRACTURE RISK ASSESSMENT**

Fracture Risk Assessment Tool from the University of Sheffield used to evaluate the 10-year probability of fracture for patients.

**EMBRYOTOX**

Embryotox – Charité's teratology/pharmacovigilance center with evidence-based monographs on 400+ medicines for use in pregnancy and breastfeeding; entries provide risk assessments, clinical recommendations and references, and may differ from package inserts; searchable by active substance. (German)

**EARLY WARNING SIGNS (ITAREPS)**

Full 10-item scale in Table 1, with both Patient and Family-Member versions, including the exact item wording and a 0–4 response scale.

**PANSS-BPRS-CGI CONVERTER**

Converts between different schizophrenia symptom rating scales (BPRS, PANSS, CGI) using equipercentile linking to standardize assessment scores across different clinical tools.

**NEUROSCIENCE-BASED NOMENCLATURE (NBN)**

Neuroscience-based Nomenclature (NbN) – ECNP-led, pharmacology/mode-of-action classification of psychotropic medicines, developed with ACNP, CINP, AsCNP and IUPHAR; provides a searchable website and free apps (including Child & Adolescent and Patients & Families versions) to standardize drug naming and support rational prescribing; updated annually.

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Thank you for your attention!