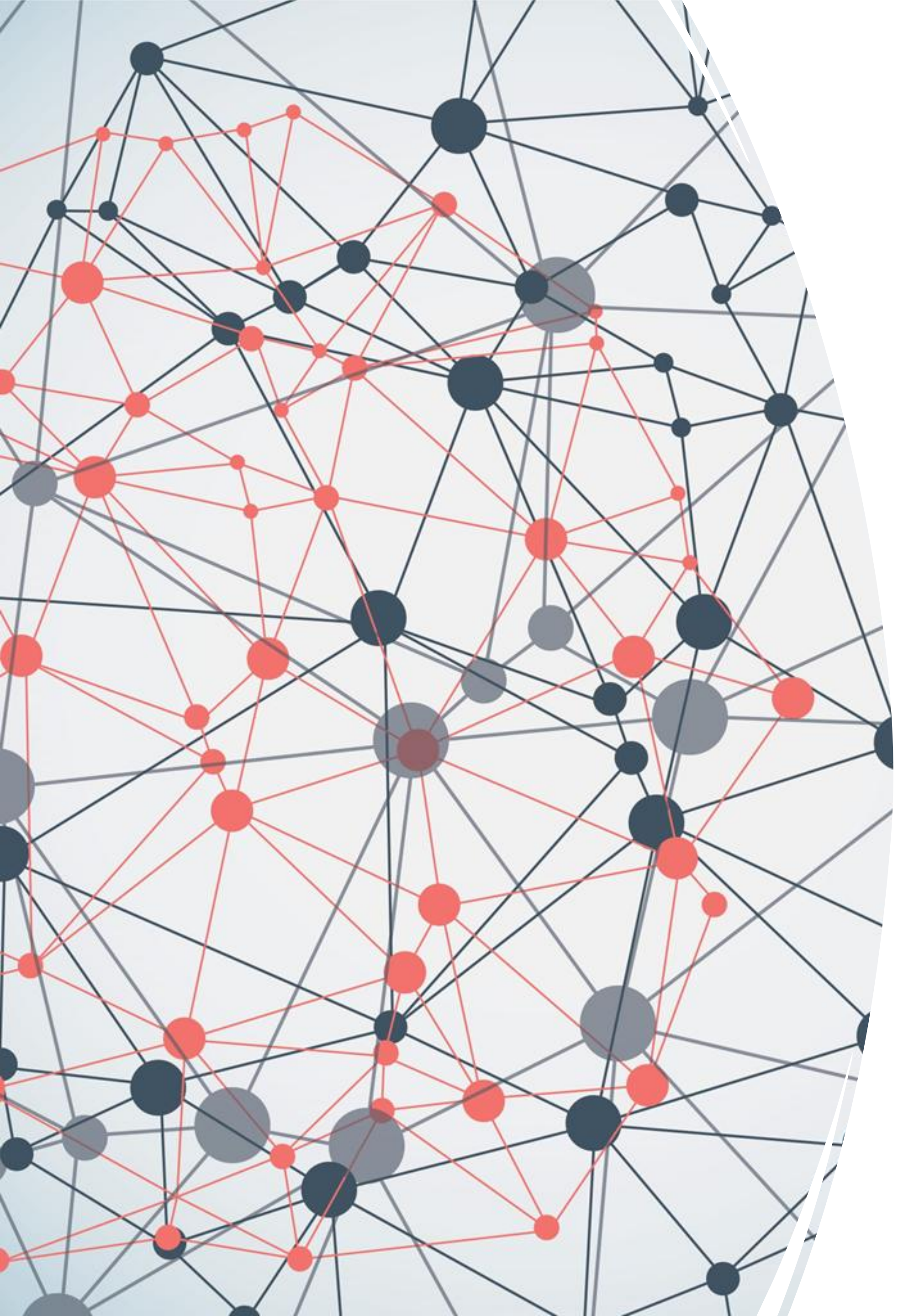

See the forest for the trees:
Comparing the efficacy and tolerability of 32 oral antipsychotics for the treatment of schizophrenia

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CSHP-BC Clinical Symposium: September 24, 2020

Presenter Disclosure

- I have no current or past relationships with commercial entities
- I have received no speaker’s fee for this learning activity

Commercial Support Disclosure

- This program has received no financial or in-kind support from any commercial or other organization

Learning Objectives

By the end of this session the learner will be able to:

- Describe the role of network meta-analyses (NMAs) in mental health literature
- Based on the results of the presented 2019 NMA, compare the efficacy and safety profiles of oral antipsychotics when used for the acute treatment of schizophrenia

Top Trial of 2019 in Mental Health

THE LANCET

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

Lancet. 2019;394:939-51

Interactive Poll

Why might a network meta-analysis approach be used to compare antipsychotics for the acute treatment of schizophrenia?

A. Indirect comparisons can be made if 2 interventions (drug A and drug B) have each been compared directly against another intervention (placebo)

B. Effect sizes can be estimated for all possible pairwise comparisons

C. All of the above

Interactive Poll

Why might a network meta-analysis approach be used to compare antipsychotics for the acute treatment of schizophrenia?

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Network Meta-analysis in Mental Health

- Evidence hierarchy: meta-analyses of randomized controlled trials
  - Limitation: evaluates pairwise comparisons only
- Mental health: head-to-head comparisons amongst all available alternatives are not available
  - Network meta-analysis evaluates data from the entire set of evidence (direct and indirect effects) to provide a global estimate of clinically important efficacy and/or safety outcomes

Heart Lung Vessel. 2015;7(2):133-42.

Methods

- Comprehensive search strategy
  - Published data: Embase, MEDLINE, PsycINFO, PubMed, BIOSIS, CENTRAL
  - Unpublished data: WHO International Clinical Trials Registry Platform, ClinicalTrials.gov
- Head-to-head and placebo-controlled randomized controlled trials (RCTs)
  - Confidence in Network Meta-analysis (CINeMA)

Lancet. 2019;394:939-51

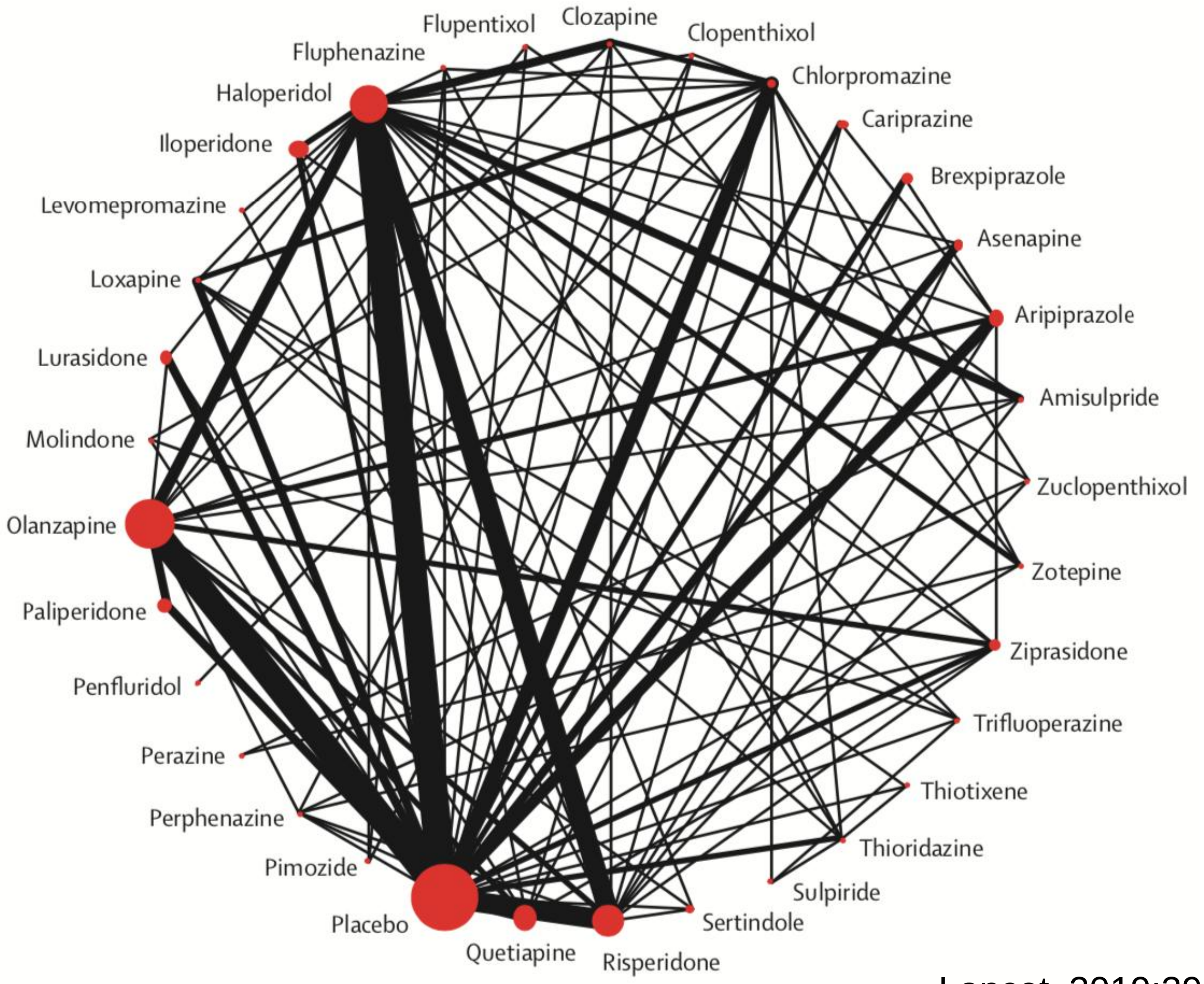
Methods

- Inclusion:
    - Acute symptoms of schizophrenia
    - Schizophreniform
    - Schizoaffective disorders
- Exclusion:
    - Treatment resistant
    - First episode
    - Predominant negative/ depressive symptoms
    - Relapse-prevention studies
    - Concomitant medical illnesses

Lancet. 2019;394:939-51

Methods

- 402 RCTs, 53 463 participants
- Average participant:
  - Mean age: 37.4 years
  - Male (56.02%)
  - Duration of illness: 11.9 years
- Interventions:
  - All second-generation antipsychotics (Europe or USA) and 17 first-generation antipsychotics
- Primary Outcome:
  - Overall change in symptoms
    - Published rating scales



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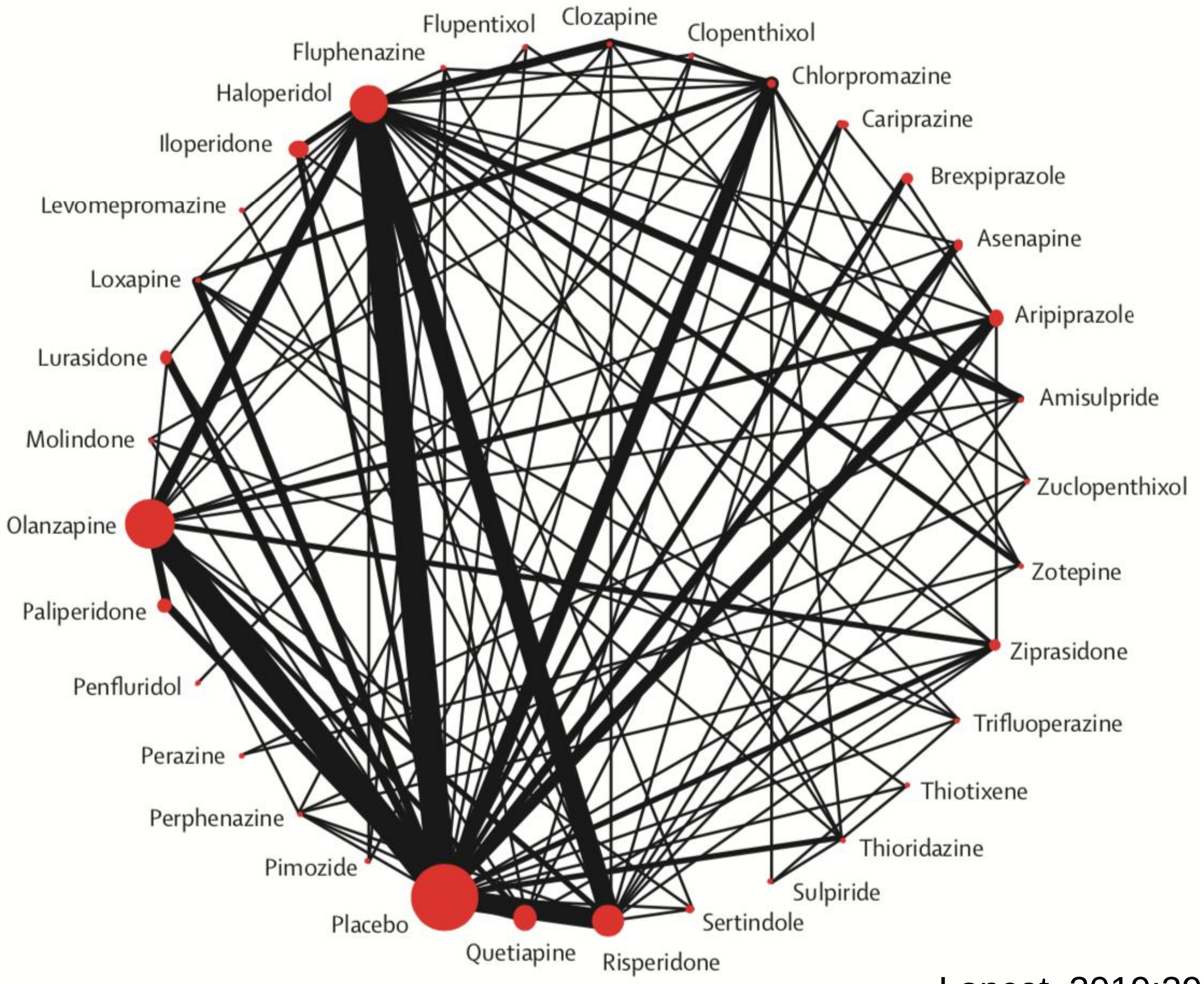
Antipsychotic Abbreviations

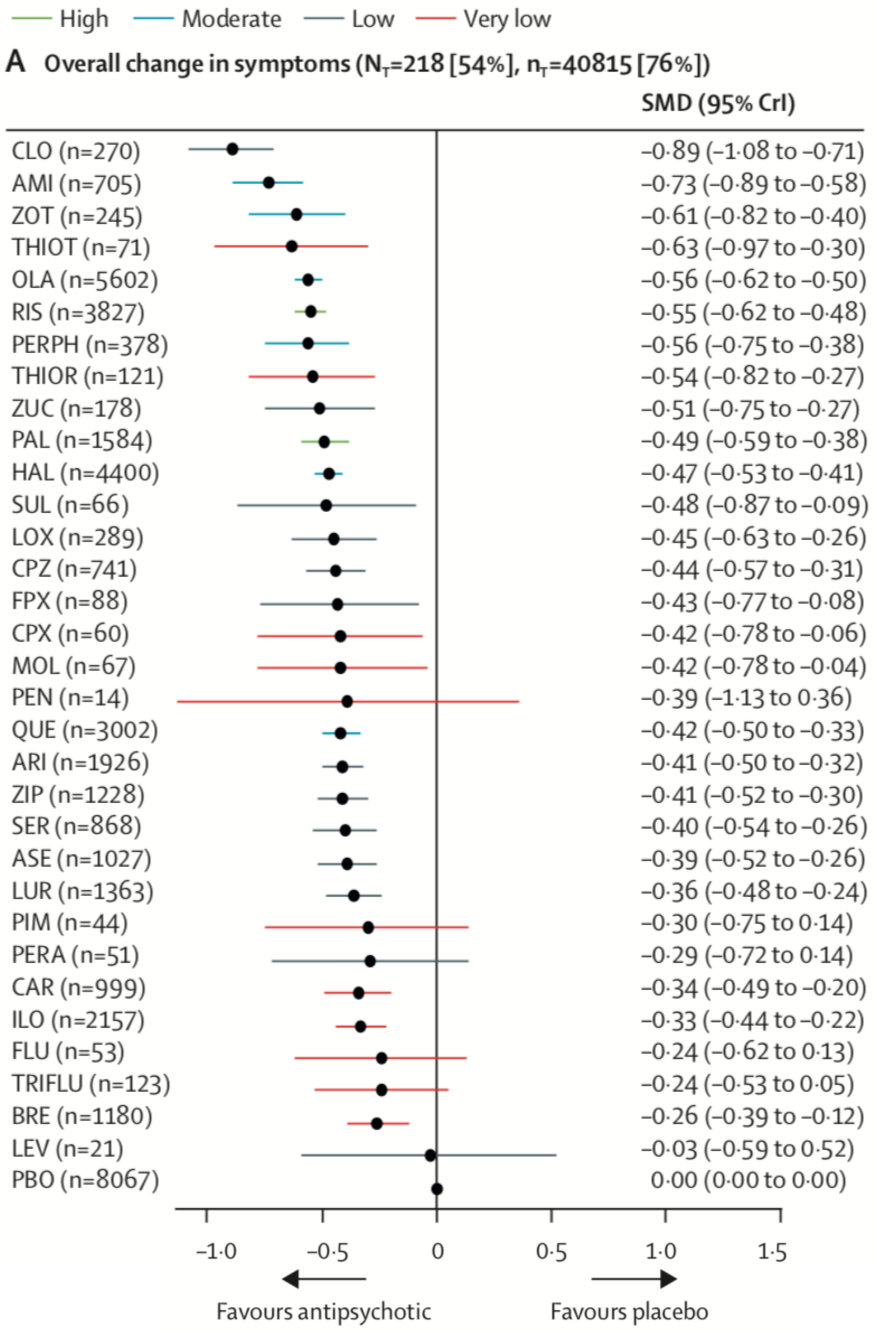
- AMI: amisulpride
- **ARI: aripiprazole**
- **ASE: asenapine**
- **BRE: brexpiprazole**
- CAR: cariprazine
- **CLO: clozapine**
- CPX: clopenthixol
- **CPZ: chlorpromazine**
- **FLU: fluphenazine**
- **FPX: flupentixol**
- **HAL: haloperidol**
- ILO: iloperidone
- LEV: levomepromazine
- **LOX: loxapine**
- **LUR: lurasidone**
- MOL: molindone
- **OLA: olanzapine**
- **PAL: paliperidone**
- PBO: placebo
- PEN: penfluridol
- PERA: perazine
- **PERPH: perphenazine**
- **PIM: pimozide**
- **QUE: quetiapine**
- **RIS: risperidone**
- SER: sertindole
- SUL: sulpiride
- THIOR: thioridazine
- THIOT: thiothixene
- **TRIFLU: trifluoperazine**
- **ZIP: ziprasidone**
- ZOT: zotepine
- **ZUC: zuclopenthixol**



Lancet. 2019;394:939-51

Results: Efficacy

- Antipsychotic drugs reduced overall symptoms more than placebo
  - Based on individual effect size estimates
  - Mean effect sizes between -0.89 and -0.03 (median -0.42)
  - <u>Confidence in the evidence</u>: low to very low
    - 75% of comparisons between antipsychotics and placebo
    - 92% of comparisons between antipsychotics



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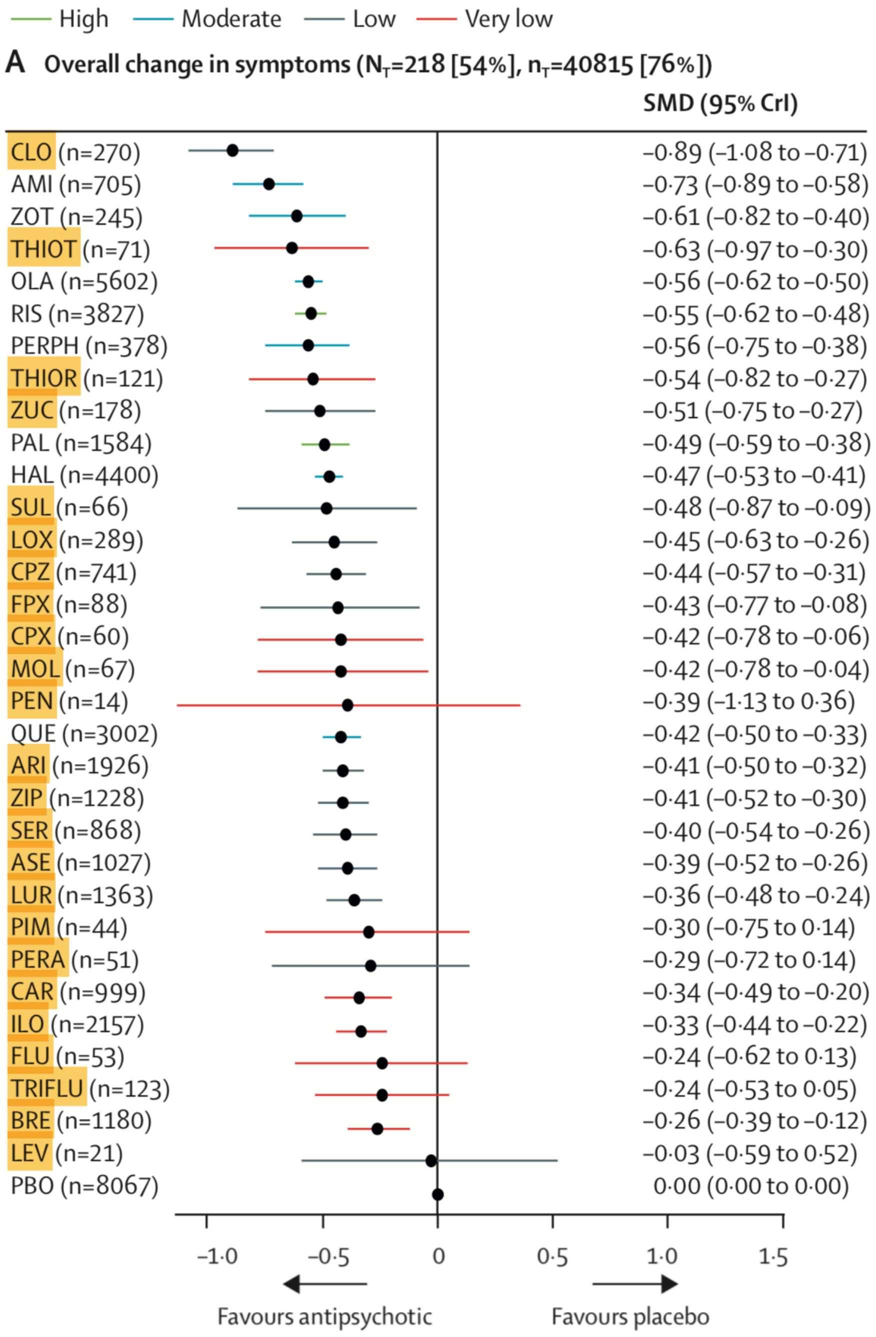
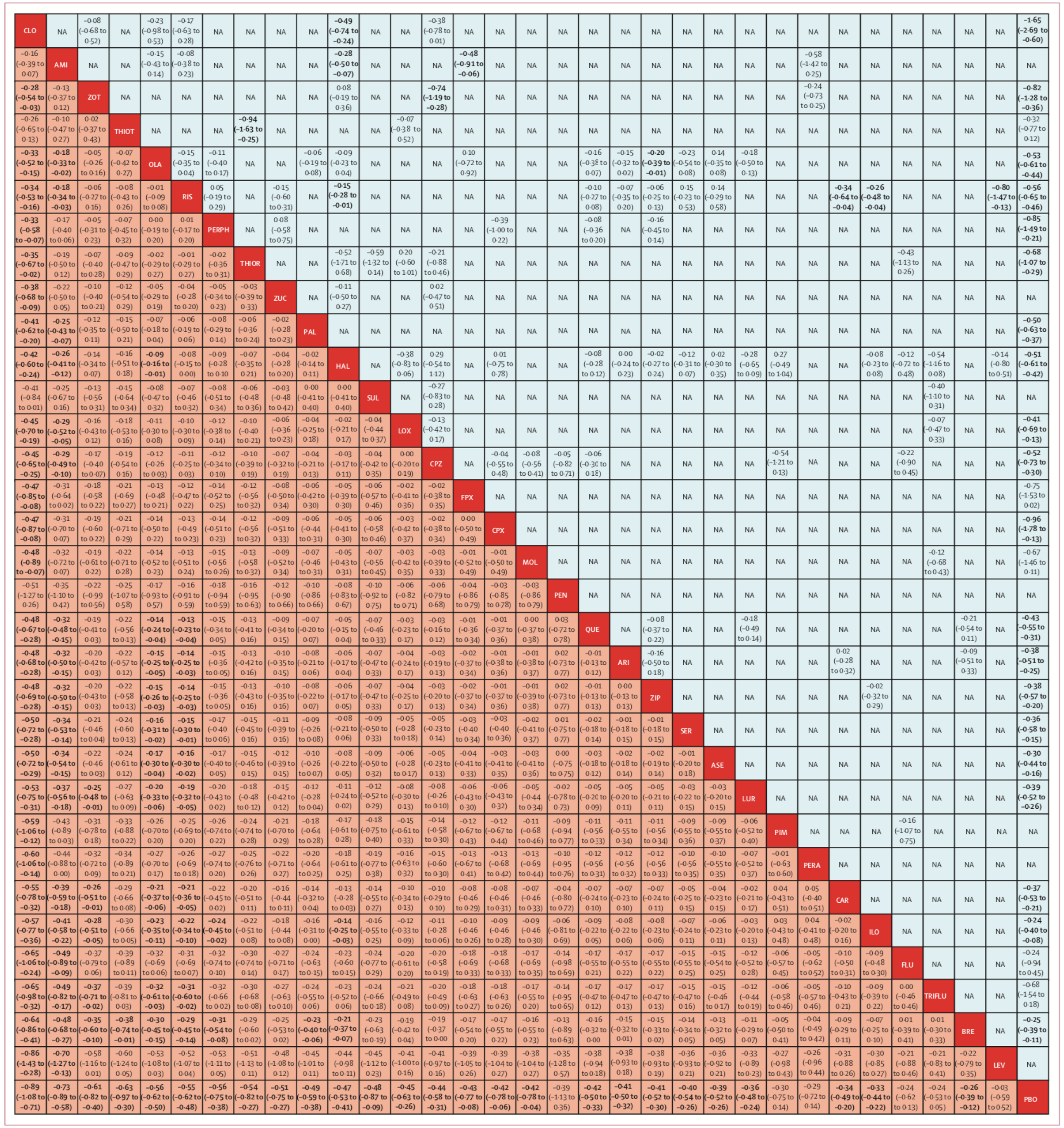


Lancet. 2019;394:939-51

Results: Efficacy

- Differences between most antipsychotics were not significant
  - Based on overlapping 95% credible intervals
  - <u>Exception</u>: clozapine, olanzapine, risperidone, amisulpride, zotepine



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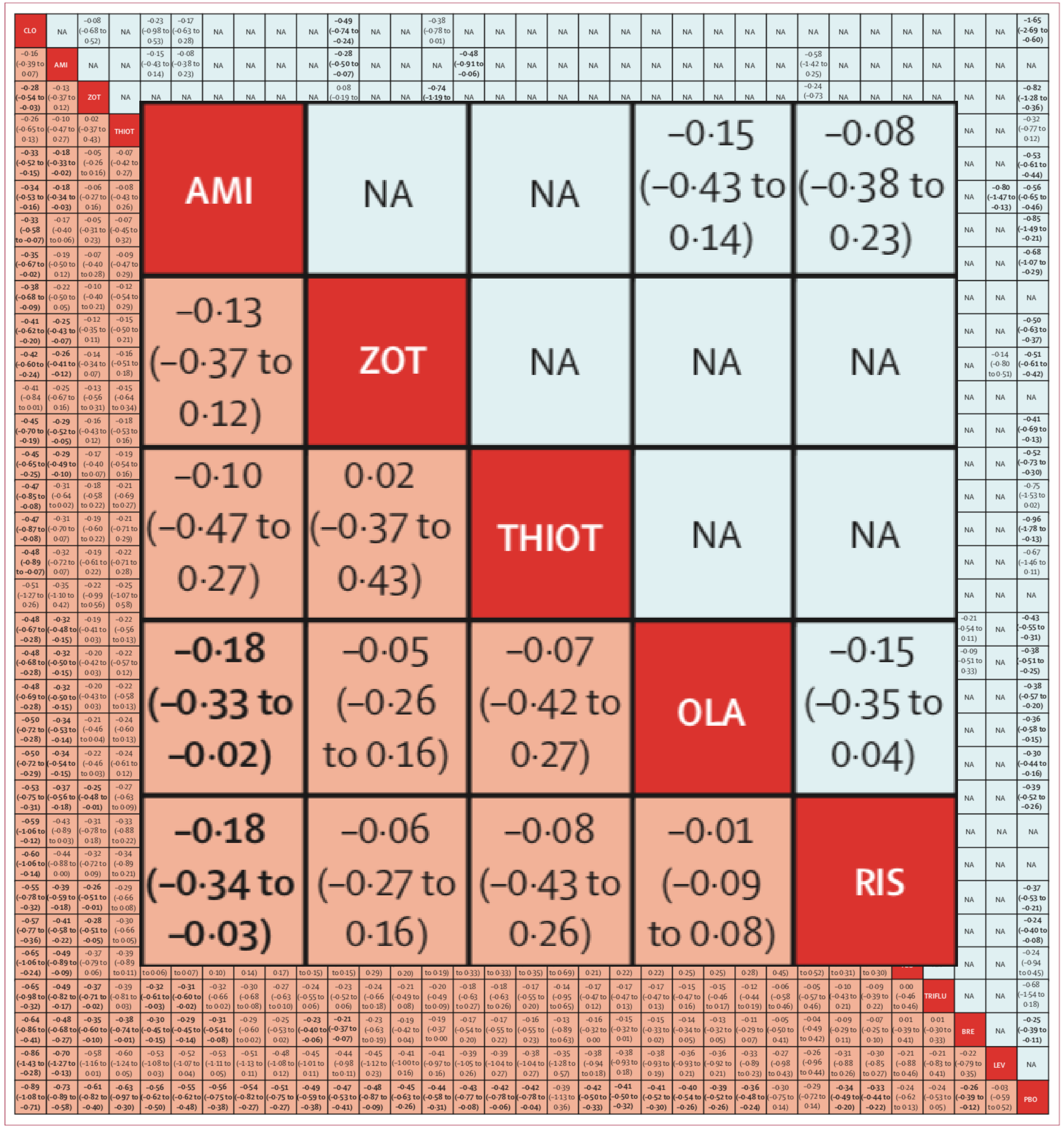

AMI	NA	NA	−0·15 (−0·43 to 0·14)	−0·08 (−0·38 to 0·23)
−0·13 (−0·37 to 0·12)	**ZOT**	NA	NA	NA
−0·10 (−0·47 to 0·27)	0·02 (−0·37 to 0·43)	**THIOT**	NA	NA
−0·18 (−0·33 to −0·02)	−0·05 (−0·26 to 0·16)	−0·07 (−0·42 to 0·27)	**OLA**	−0·15 (−0·35 to 0·04)
−0·18 (−0·34 to −0·03)	−0·06 (−0·27 to 0·16)	−0·08 (−0·43 to 0·26)	−0·01 (−0·09 to 0·08)	**RIS**

Abbreviation NA: not available

Lancet. 2019;394:939-51

Results: Safety

- Antipsychotics very often scored worse than placebo for side-effect outcomes
- Extrapyramidal side-effects
  - In general, greater risk with first-generation antipsychotics
    - E.g. haloperidol, loxapine, flupentixol, zuclopenthixol

Lancet. 2019;394:939-51

Results: Safety

- Weight gain
  - In general, greater weight gain with second-generation antipsychotics
  - Olanzapine>quetiapine>paliperidone> risperidone
- QTc prolongation
  - Lurasidone and the partial dopamine agonists were most benign
  - Similar risk when comparing risperidone, olanzapine, quetiapine
  - Highest risk with ziprasidone

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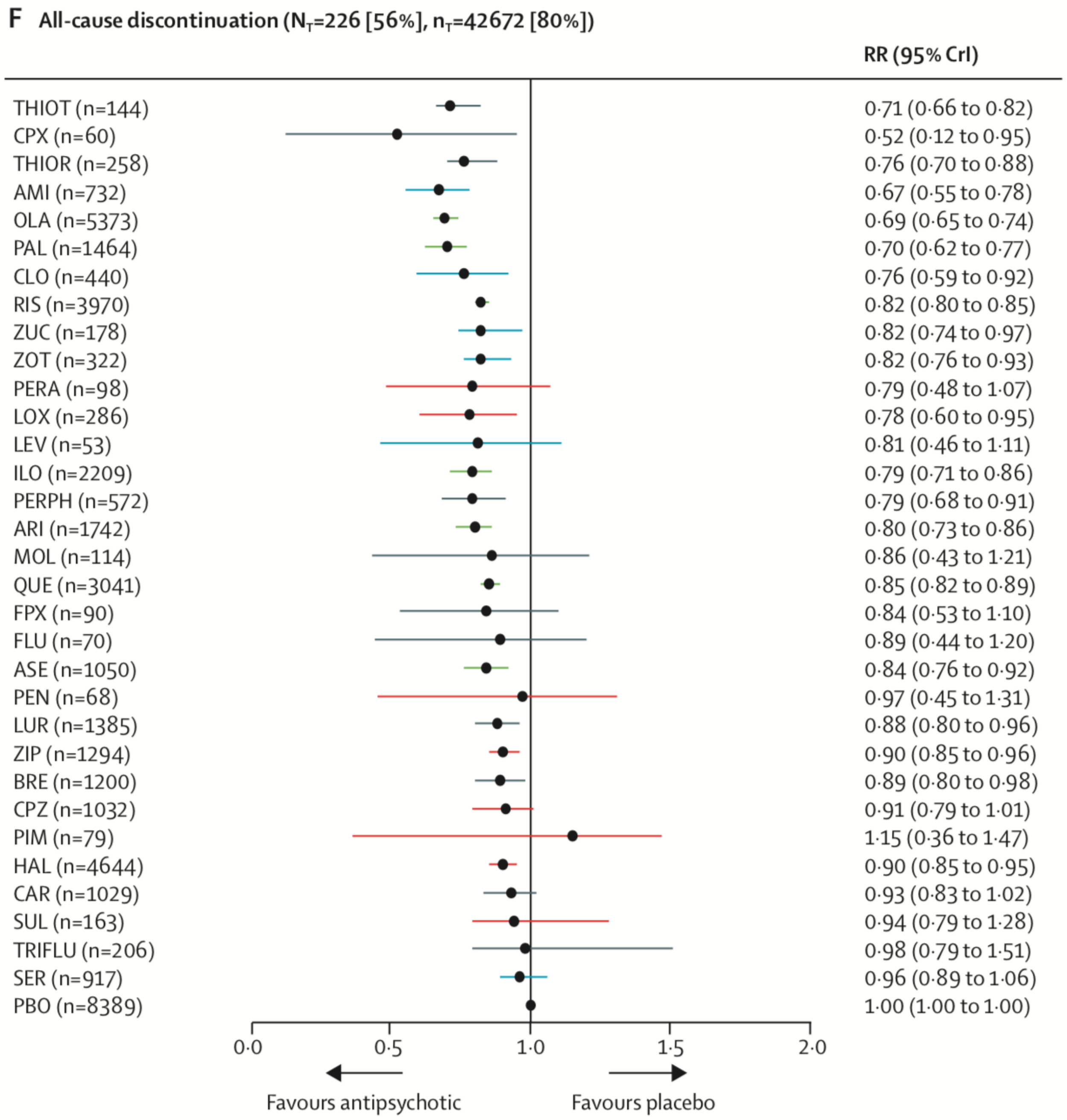
Results

- All-cause discontinuation
  - Intervention discontinued less often than placebo owing to beneficial efficacy



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Limitations

- Overall risk of bias was rated high for 23% of studies
- Confidence in the evidence was variable across outcomes
  - Overall change in symptoms: low to very low
  - Weight gain in kilograms: high to moderate
- Efficacy measurements are based on subjective rating scales
  - Positive and Negative Syndrome Scale (PANSS)
  - Brief Psychiatric Rating Scale (BPRS)

Lancet. 2019;394:939-51

Limitations

- Studies including older antipsychotics had less placebo response than those with newer antipsychotics
- Baseline severity of schizophrenia in studies differed by individual antipsychotic

Above limitations were addressed by meta-regressions and sensitivity analyses of the primary outcome (excluded studies with less than 100 participants)

Lancet. 2019;394:939-51

Clinical Considerations

- Studies excluded patients with concurrent substance use disorder[1]
  - Substance use disorder as a comorbidity of schizophrenia is highly prevalent (41.7%)[2]
  - Substance use disorder may also affect medication adherence – crucial to consider potential benefit of treating schizophrenia and providing concurrent addictions support (e.g. naltrexone, methadone, buprenorphine/naloxone)

[1]Lancet. 2020;395:1902.
[2]Drug Alcohol Depend. 2018;191:234-58.

Conclusions

- For the acute treatment of schizophrenia:
  - Overall, oral antipsychotics are more effective than placebo and the available evidence supports their use
  - Differences in the adverse effect profiles of oral antipsychotics are more discernible than differences in efficacy

- Pharmacists are partners to assist in making informed choices
  - Tolerability of adverse effects and protecting a patient's physical health should be emphasized

Lancet. 2019;394 (10202):900-2.

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Thank you!