Current controversies in the pharmacological treatment of psychosis

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Agenda

- Disclosures
- Introduction
- Controversies
  - Efficacy and effectiveness
  - Tolerability
  - Route of administration
  - Mechanisms of action
  - Neurotoxicity
- Conclusions
- Where do we go from here?

Disclosures

- Until 20111:Honoraria for lectures given in meetings arranged by Bristol-Myers Squibb, Eli Lilly, and AstraZeneca; contribution to an information brochure by Eli Lilly; reimbursements by the Eli Lilly Company and the Janssen Cilag Company for attending 2 conferences.
- PI of Bergen psychosis project 2/ Best Intro study
- National coordinator EULAST

History

- 1952: Demonstration of the antipsychotic properties of chlorpromazine in monotherapy
- 1954: First description of acute extrapyramidal side effects
- 1958: Haloperidol
- 1959: Tardive dyskinesias described
- 1959: Clozapine
- 1962: Dopaminergic blockage by antipsychotics demonstrated
- 1974: 8 deaths in Finland by clozapine-associated agranulocytosis
- 1990 →: Reintroduction of clozapine in the US; Second Generation Antipsychotics (SGAs)/ Atypicals

Shen WW. Compr Psychiatry 1999;40:407-14;
Hippius H. J Clin Psychiatry 1999;60(suppl 12):22-3.

Antipsychotic drugs in Norway

- First generation (**FGA**)
  - Levomepromazine (Nozinan)
  - Chlorprothixene (Truxal)
  - Perfenazine (Trilafon)
  - Zuclopenthixol (Cisordinol)
  - Flupentixol (Fluanxol)
  - Haloperidol (Haldol)
  - Amisulpride (Solian)
- Second generation (**SGA**)
  - clozapine (Leponex*)
  - risperidone (Risperdal)
  - Olanzapine (Zyprexa)
  - Quetiapine (Seroquel)
  - Ziprasidone (Zeldox)
  - Sertindol (Serdolect*)
  - Paliperidone palmitat (Xeplion)
  - Aripiprazol (Abilify)
  - Lurasidone (Latuda)

Controversy # 1

- How efficacious are antipsychotics?
  - Acute treatment
  - Relapse prevention

Levels of evidence

Level 1	Systematic review of RCTs or n-of-1 trials
Level 2	RCT or observational study with dramatic effect
Level 3	Non-randomized controlled cohort/ follow-up study
Level 4	Case-series, case-control, or historically controlled studies
Level 5	Mechanism-based reasoning

OCEBM Levels of Evidence Working Group. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine.

Effect Size

- Rule of thumb
  - 0.2 ~ small
  - 0.5 ~ moderate
  - 0.8 ~ large

Cohen J, 1988

Acute treatment

Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis

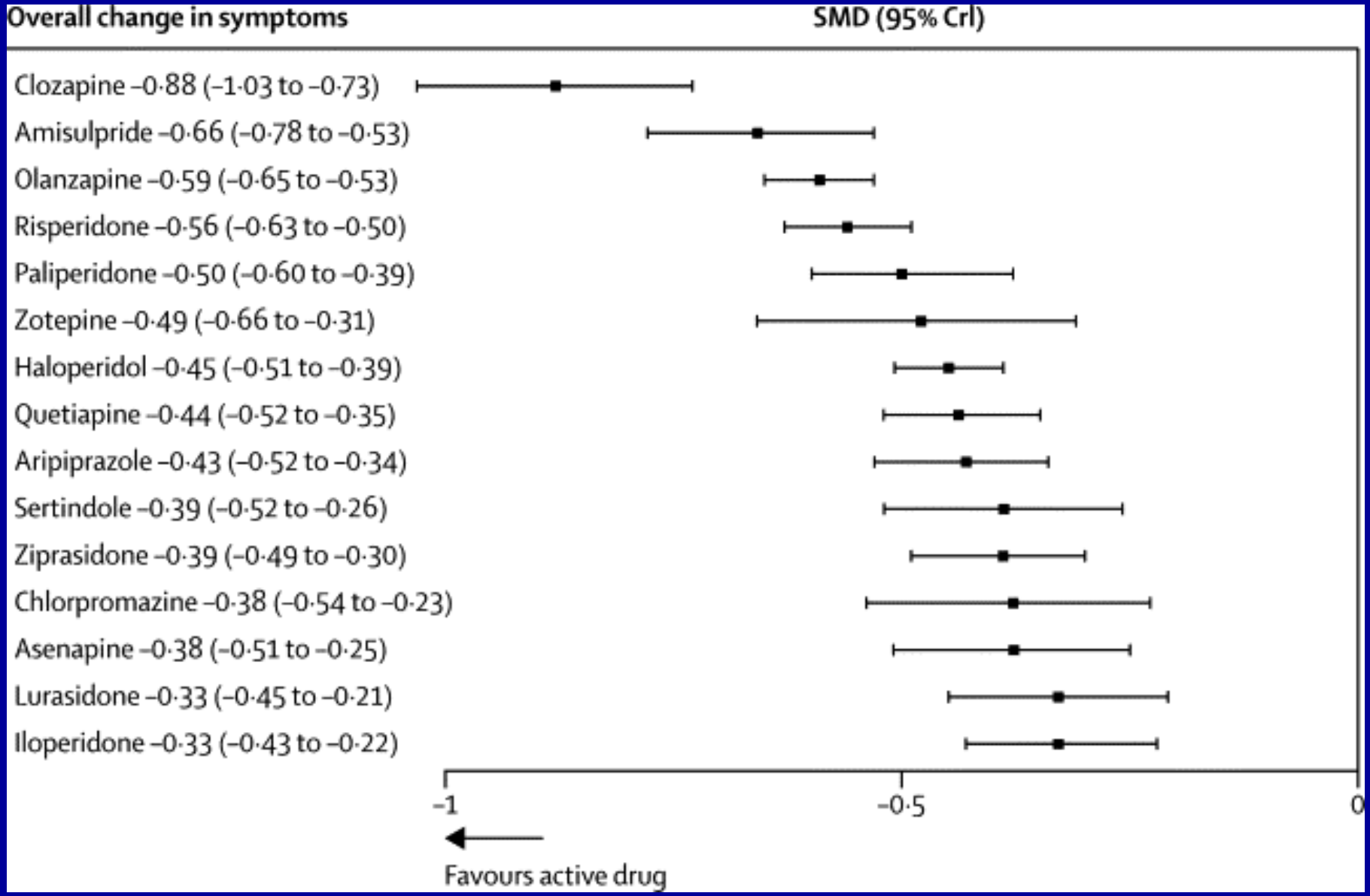
Stefan Leucht, Andrea Cipriani, Loukia Spineli, Dimitris Mavridis, Deniz Örey, Franziska Richter, Myrto Samara, Corrado Barbui, Rolf R Engel, John R Geddes, Werner Kissling, Marko Paul Stapf, Bettina Lässig, Georgia Salanti, John M Davis

Summary

Background The question of which antipsychotic drug should be preferred for the treatment of schizophrenia is controversial, and conventional pairwise meta-analyses cannot provide a hierarchy based on the randomised evidence. We aimed to integrate the available evidence to create hierarchies of the comparative efficacy, risk of all-cause discontinuation, and major side-effects of antipsychotic drugs.

Lancet 2013; 382: 951–62
Published Online
June 27, 2013
http://dx.doi.org/10.1016/S0140-6736(13)60733-3

- Acute treatment, 6 weeks
- Schizophrenia and related
- Mean duration of illness 12 years
- 212 studies, blinded RCT
- N=43049



Leucht et al. Lancet 2013

Summing up - antipsychotic efficacy vs. placebo

- Number Needed to Treat 2-6
- Effect Size approx 0.5

Leucht S et al. Lancet 2013;382:952-61;
Leucht S et al. Mol Psychiatry 2009;14:429-47

Relapse prevention

Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis

Stefan Leucht, Magdolna Tardy, Katja Komossa, Stephan Heres, Werner Kissling, Georgia Salanti, John M Davis

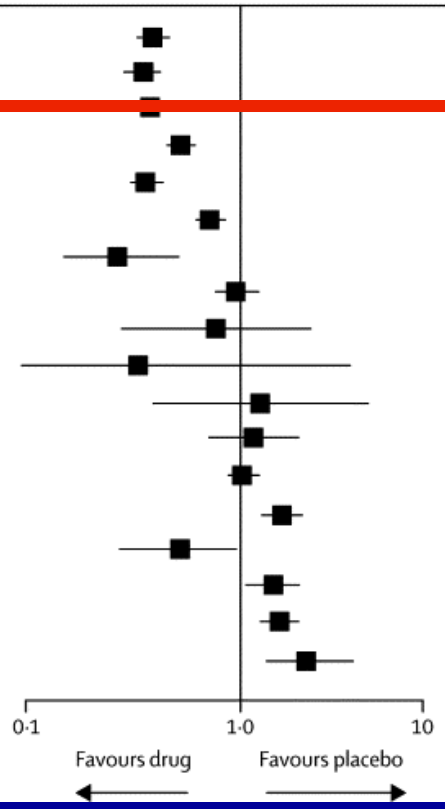
Summary

Background Relapse prevention with antipsychotic drugs compared with placebo in patients with schizophrenia has

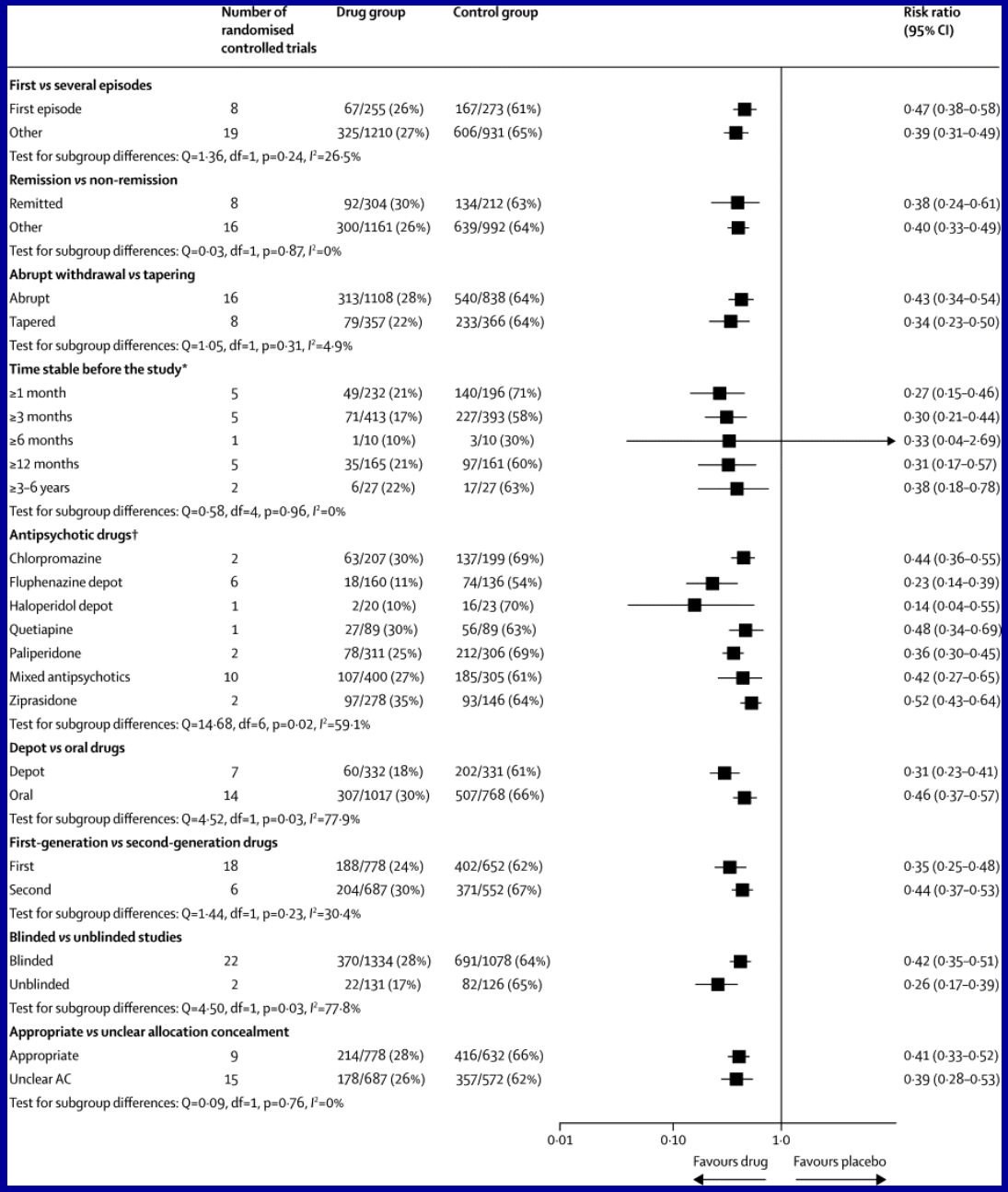
Lancet 2012; 379: 2063–71

- Relapse, 7-12 months
- Schizophrenia
- Mean duration of illness 13.6 years
- 116 reports from 65 blinded RCT
- N=6493

	Number of studies included	Drug group	Control group	Mean study duration* (months)	Risk ratio (95% CI)	Absolute difference (95% CI)	NNTB/H (95% CI)
Relapse 7–12 months	24	392/1465 (27%)	773/1204 (64%)	11	0·40 (0·33 to 0·49)	−0·39 (−0·46 to −0·32)	3 (2 to 3)
Relapse independent of duration	62	744/3395 (22%)	1718/2997 (57%)	9	0·35 (0·29 to 0·41)	−0·38 (−0·43 to −0·33)	3 (2 to 3)
Dropout for any reason	57	802/2642 (30%)	1130/2076 (54%)	9	0·53 (0·46 to 0·61)	−0·24 (−0·30 to −0·17)	4 (3 to 6)
Dropout because of inefficacy	46	412/2539 (16%)	830/2007 (41%)	8	0·37 (0·31 to 0·44)	−0·27 (−0·34 to −0·19)	4 (3 to 5)
Participants unimproved/worse	14	614/880 (70%)	569/644 (88%)	5	0·73 (0·64 to 0·84)	−0·25 (0·35 to 0·14)	4 (3 to 7)
Violent/aggressive behaviour	5	9/403 (2%)	34/277 (12%)	8	0·27 (0·15 to 0·52)	−0·09 (−0·17 to −0·01)	11 (6 to 100)
Participants employed	2	63/130 (48%)	65/129 (50%)	11	0·96 (0·75 to 1·23)	−0·02 (−0·14 to 0·10)	50 (H7 to B10)†
Death (any)	14	5/1240 (<1%)	7/1116 (1%)	7	0·77 (0·28 to 2·11)	0·00 (−0·01 to 0·00)	∞
Suicide	8	0/1021	2/920 (<1%)	6	0·34 (0·04 to 3·28)	0·00 (−0·01 to 0·00)	∞
Death from natural causes	14	5/1272 (1%)	3/1129 (<1%)	7	1·24 (0·39 to 3·97)	0·00 (0·00 to 0·01)	∞
Dropout because of AE	43	129/2437 (5%)	78/1896 (4%)	8	1·16 (0·70 to 1·91)	0·00 (−0·01 to 0·02)	∞
At least one AE	10	575/1188 (48%)	450/996 (45%)	7	1·01 (0·87 to 1·18)	0·01 (−0·06 to 0·08)	100 (H17 to B13)†
At least one MD	22	304/1901 (16%)	134/1510 (9%)	7	1·55 (1·25 to 1·93)	0·06 (0·03 to 0·10)	17 (10 to 33)
Dyskinesia	13	18/1051 (2%)	37/769 (5%)	9	0·52 (0·28 to 0·97)	−0·01 (−0·02 to 0·01)	100 (H50 to B100)†
Use of antiparkinsonian medication	7	182/748 (24%)	90/569 (16%)	7	1·40 (1·03 to 1·89)	0·09 (0·02 to 0·16)	11 (6 to 50)
Sedation	10	158/1174 (13%)	85/972 (9%)	6	1·50 (1·22 to 1·84)	0·05 (0·00 to 0·10)	20 (B=∞ to H10)†
Weight gain	10	128/1231 (10%)	61/1090 (6%)	7	2·07 (2·31 to 3·25)	0·05 (0·03 to 0·07)	20 (14 to 33)



Leucht et al. Lancet 2012



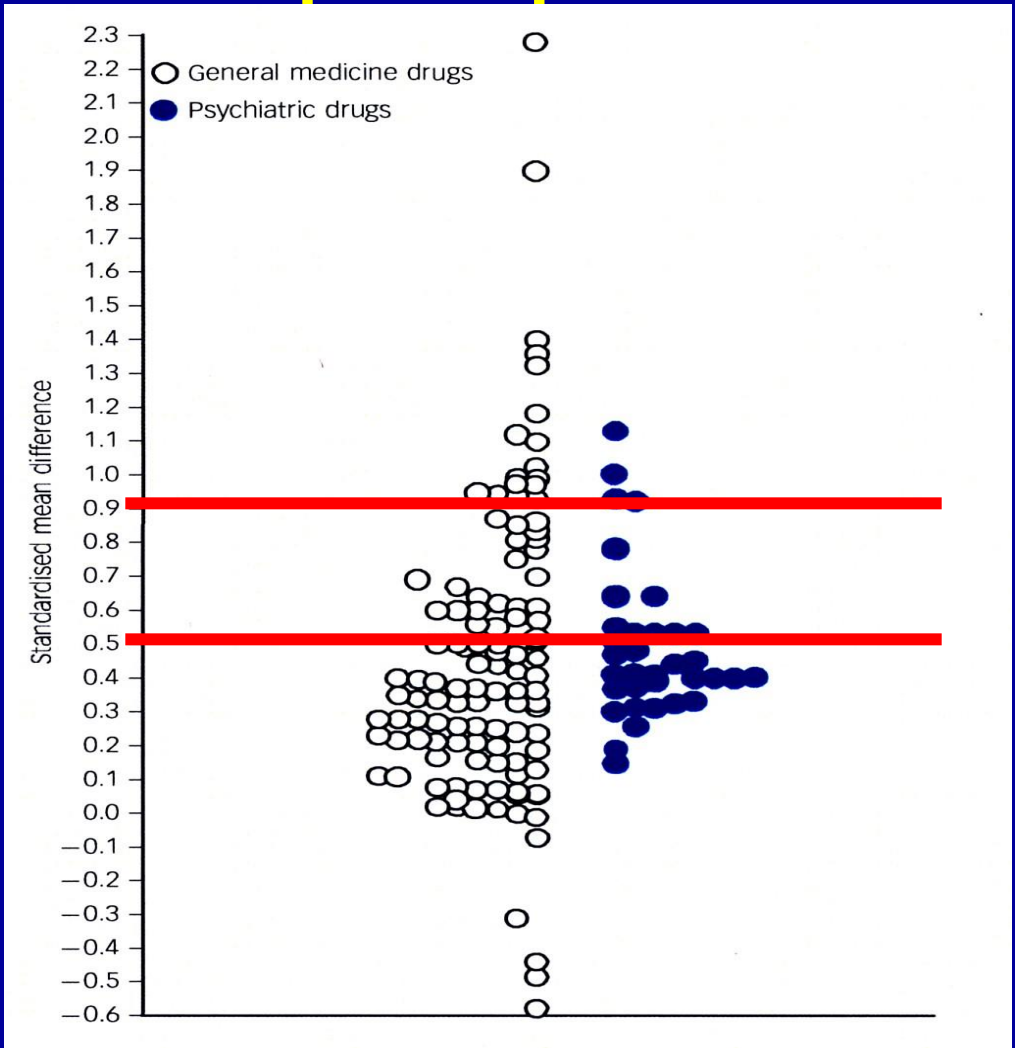
Leucht et al. Lancet 2012

Summing up - relapse prevention

- Number Needed to Treat 3
- Effect Size approx 0.9

Leucht S et al. Br J Psychiatry 2012;200:97-106

Effect Sizes – put into perspectice



Leucht S et al. Br J Psychiatry 2012;200:97-106

Controversy # 2

- Are all antipsychotics equally efficacious (except clozapine)?

Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis

Stefan Leucht, Andrea Cipriani, Loukia Spineli, Dimitris Mavridis, Deniz Örey, Franziska Richter, Myrto Samara, Corrado Barbui, Rolf R Engel, John R Geddes, Werner Kissling, Marko Paul Stapf, Bettina Lässig, Georgia Salanti, John M Davis

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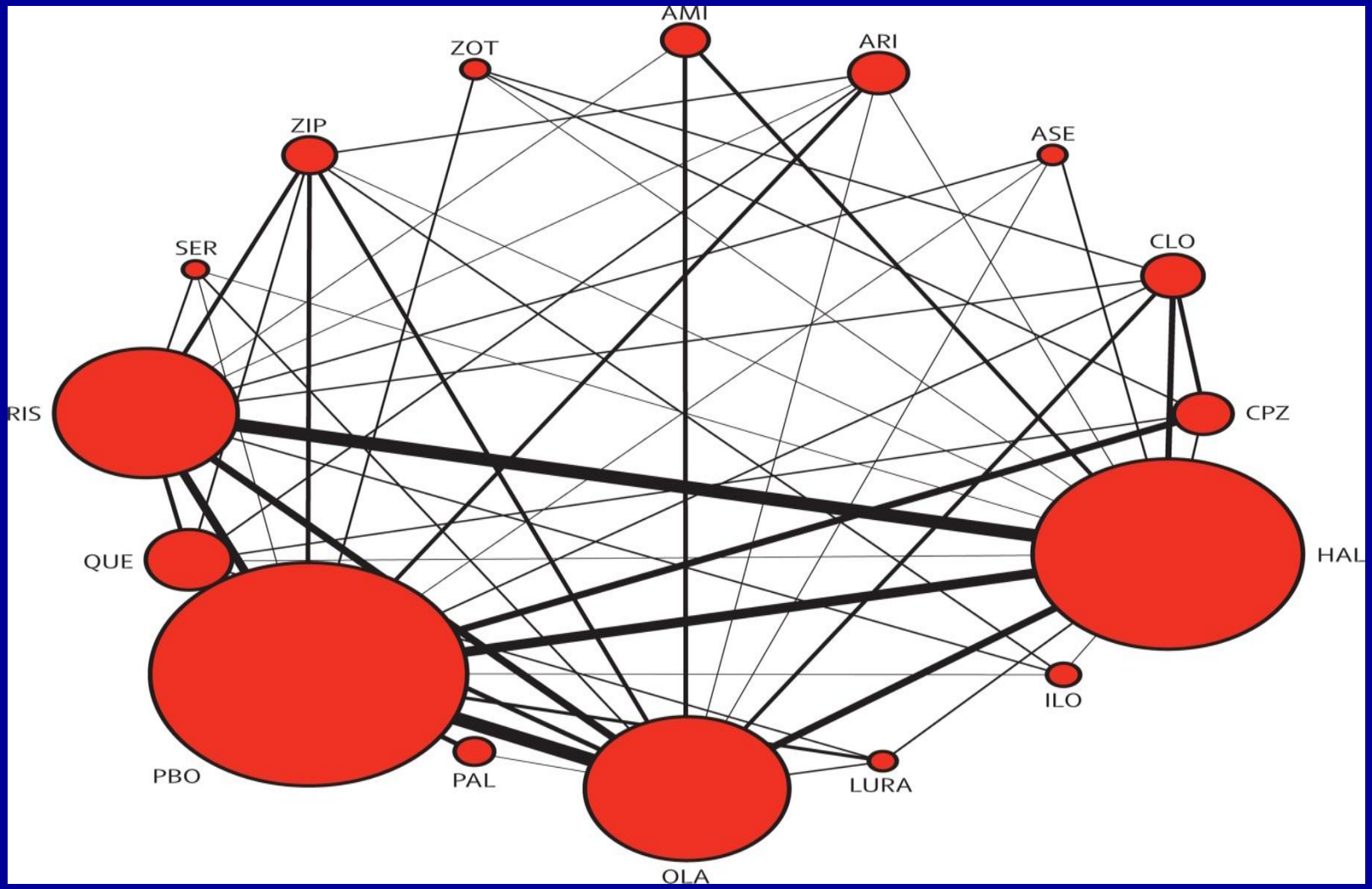
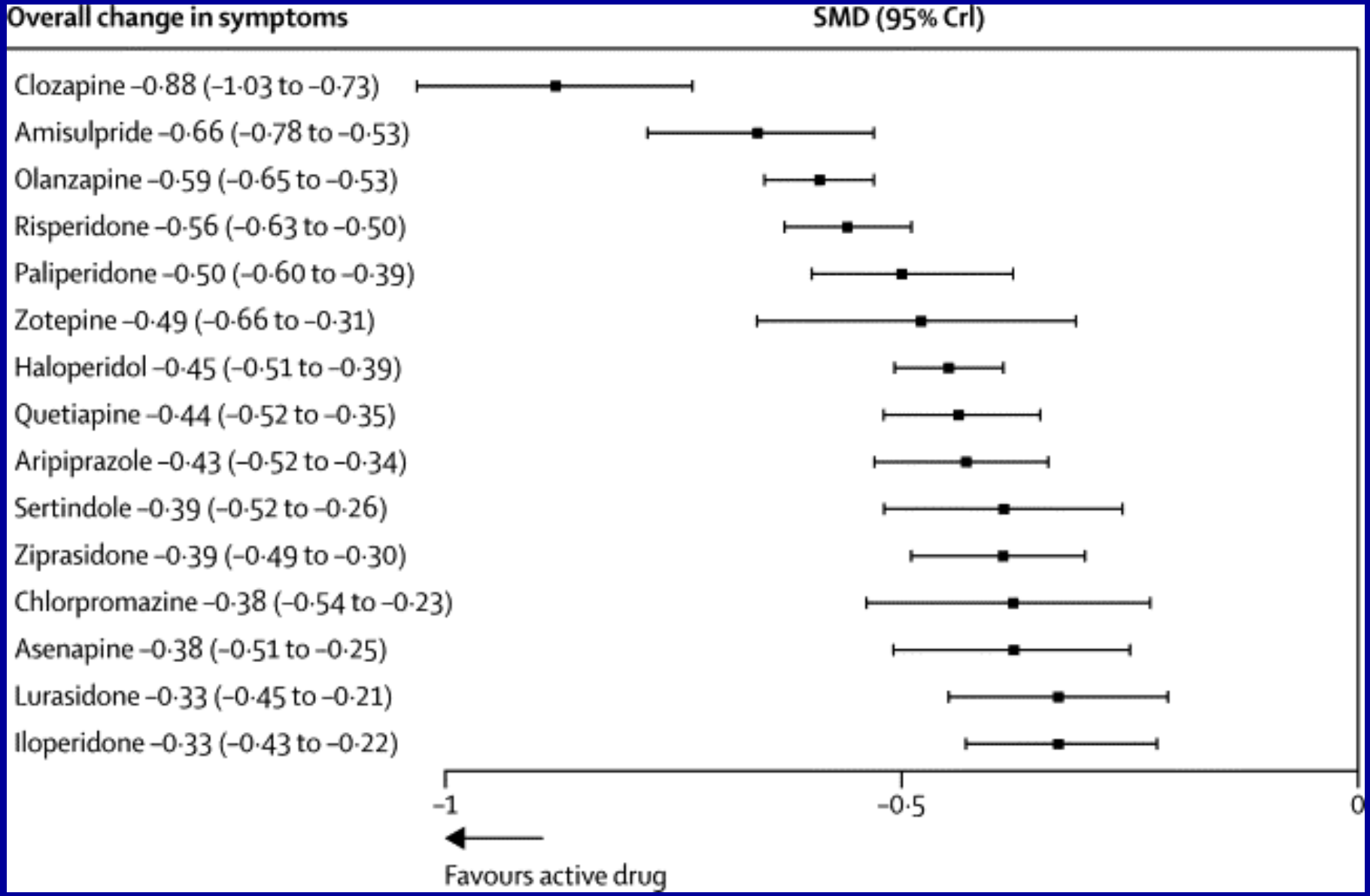
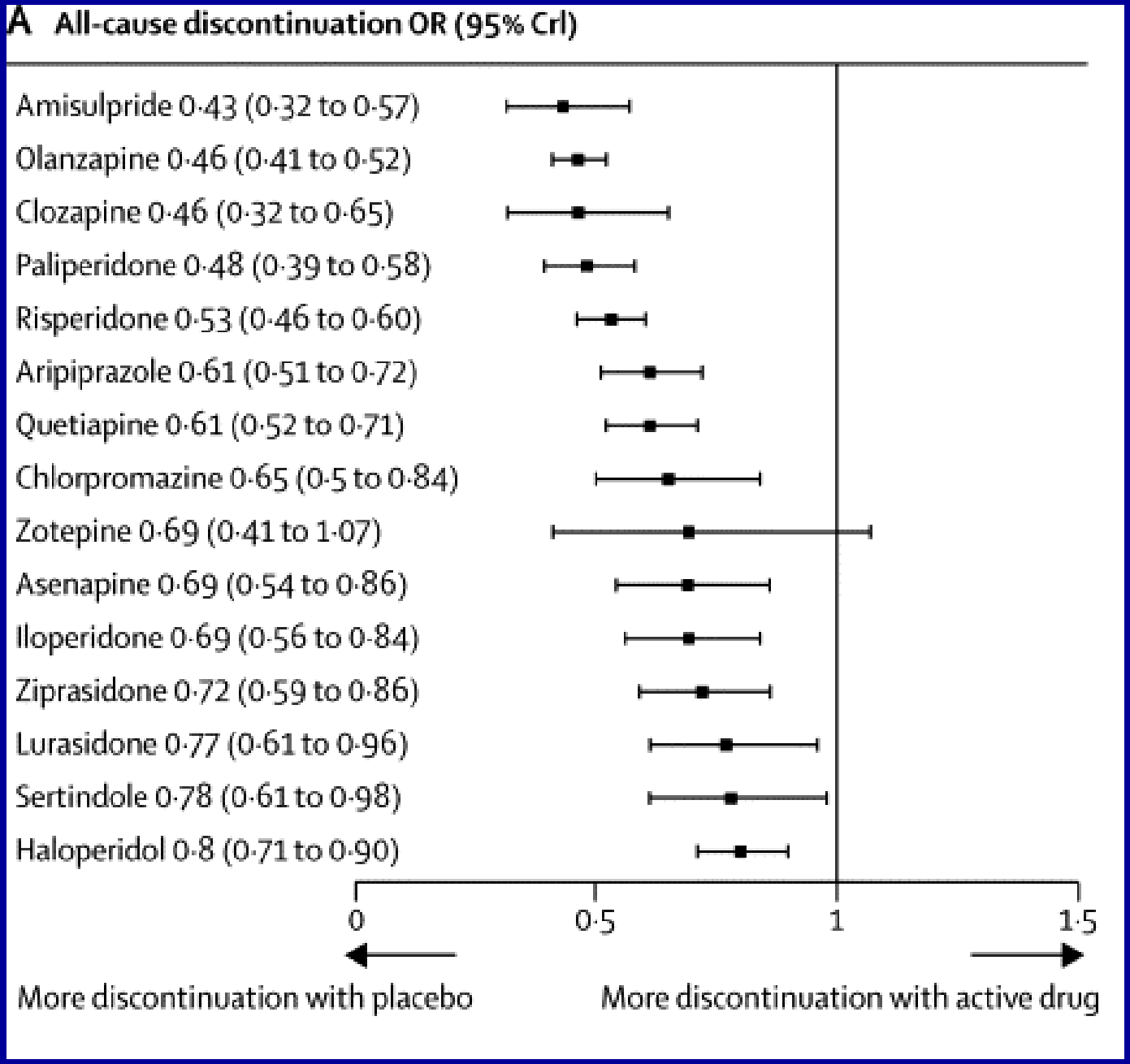


Leucht et al. Lancet 2013



Leucht et al. Lancet 2013


A All-cause discontinuation OR (95% CrI)
Amisulpride 0·43 (0·32 to 0·57)
Olanzapine 0·46 (0·41 to 0·52)
Clozapine 0·46 (0·32 to 0·65)
Paliperidone 0·48 (0·39 to 0·58)
Risperidone 0·53 (0·46 to 0·60)
Aripiprazole 0·61 (0·51 to 0·72)
Quetiapine 0·61 (0·52 to 0·71)
Chlorpromazine 0·65 (0·5 to 0·84)
Zotepine 0·69 (0·41 to 1·07)
Asenapine 0·69 (0·54 to 0·86)
Iloperidone 0·69 (0·56 to 0·84)
Ziprasidone 0·72 (0·59 to 0·86)
Lurasidone 0·77 (0·61 to 0·96)
Sertindole 0·78 (0·61 to 0·98)
Haloperidol 0·8 (0·71 to 0·90)
0
0·5
1
1·5
More discontinuation with placebo
More discontinuation with active drug

Summing up
Head-to-head antipsychotics

"We interpret the meta-analyses such that overall clozapine, amisulpride, olanzapine and risperidone may be somewhat more efficacious than FGAs and other SGAs…"

Leucht s et al. Int J Neuropsychopharmacol 2011;14:269-84

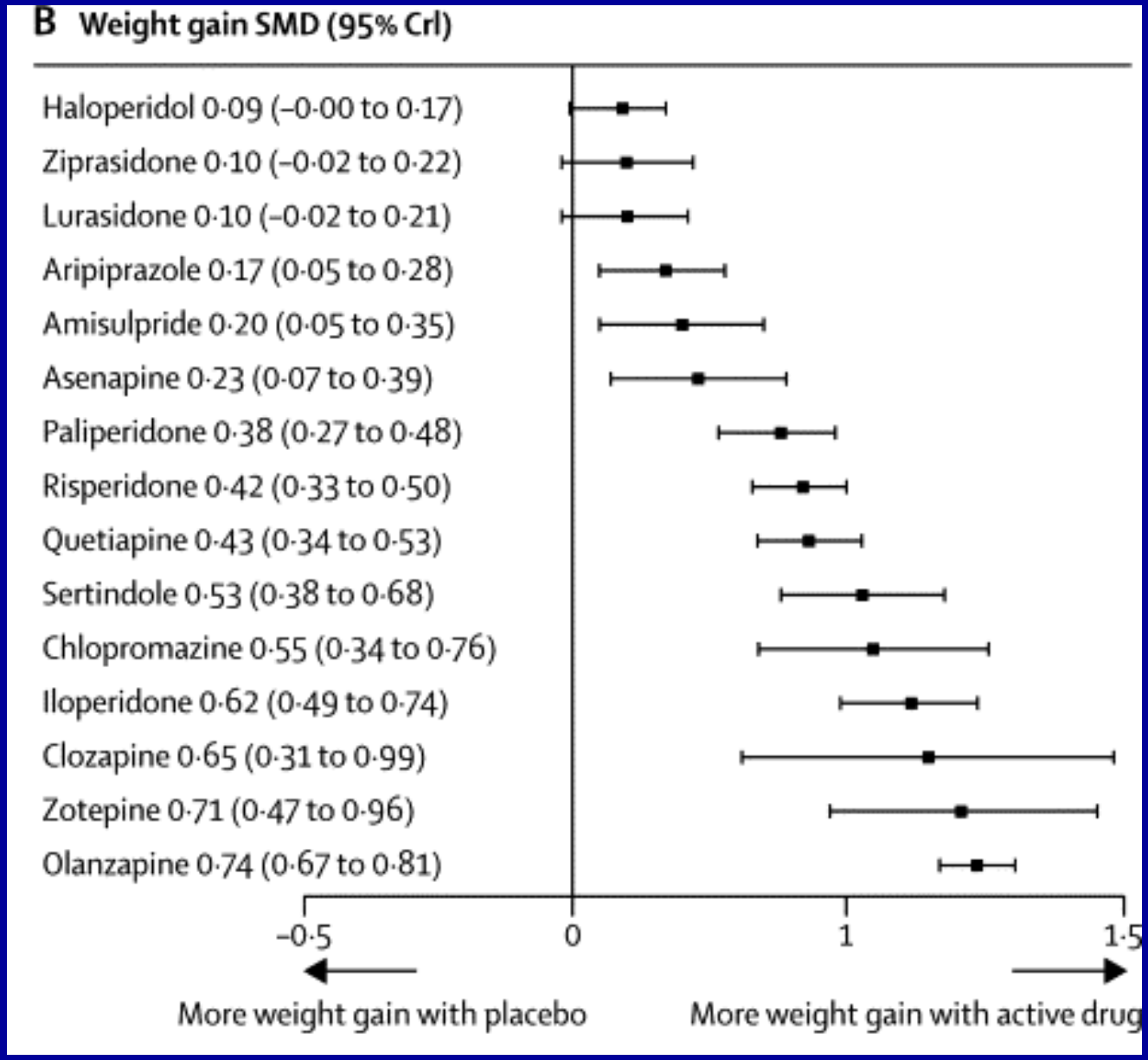
"To summarize, in FES, olanzapine, amisulpride and, less so, risperidone and quetiapine showed superior efficacy, greater treatment persistence and less EPS than FGAs."

Effect Size differences 0.1-0.5

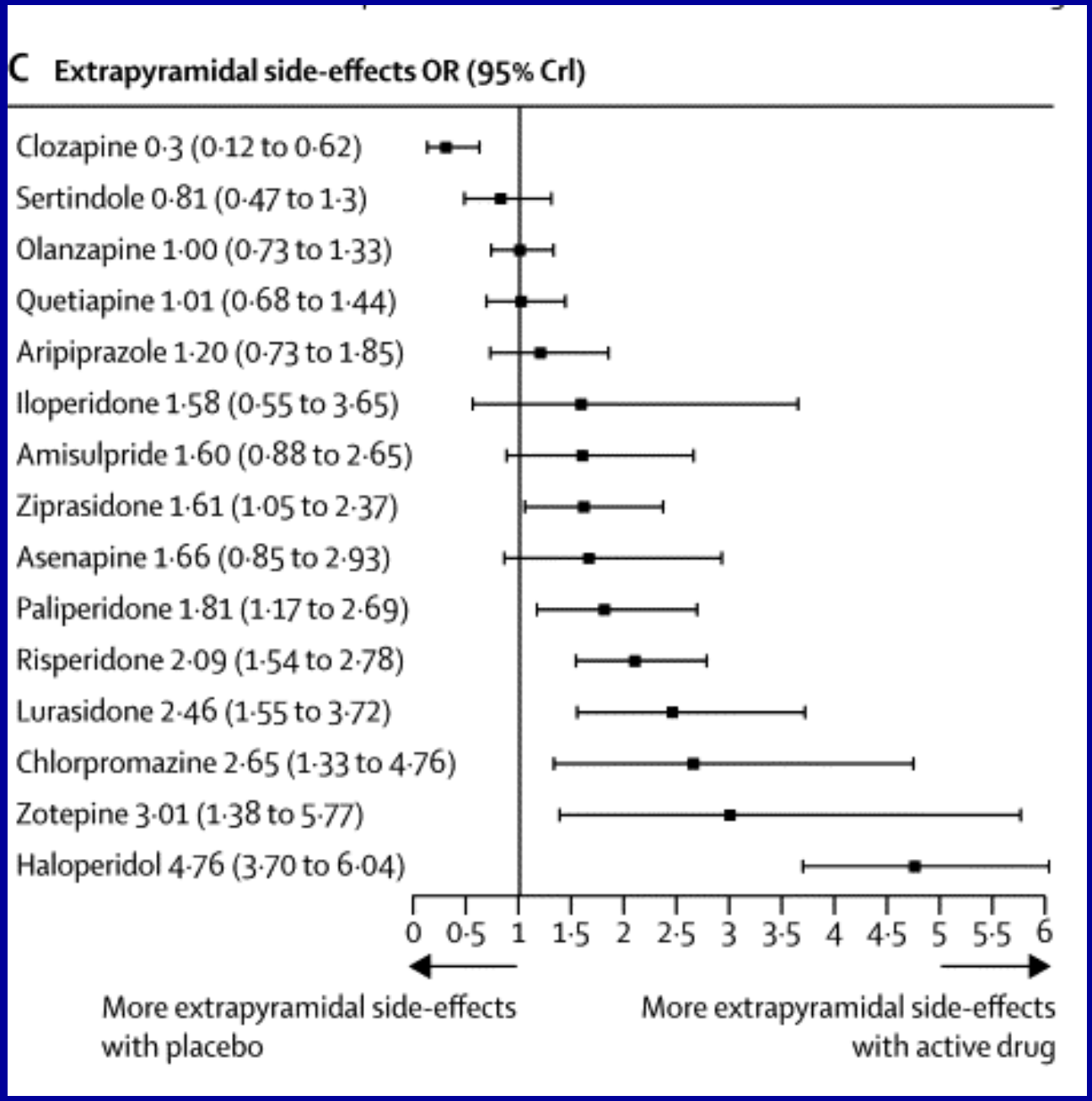
Leucht S et al. Lancet 2013;382:853-62; Zhang JP et al. Int J Neuropsychopharmacol 2012;Dec 3:1-14; Citrome L. Expert Opin Pharmacother 2012;13:1545-73; Leucht S et al., Am J Psychiatry 2009;166:152-63

Controversy # 3

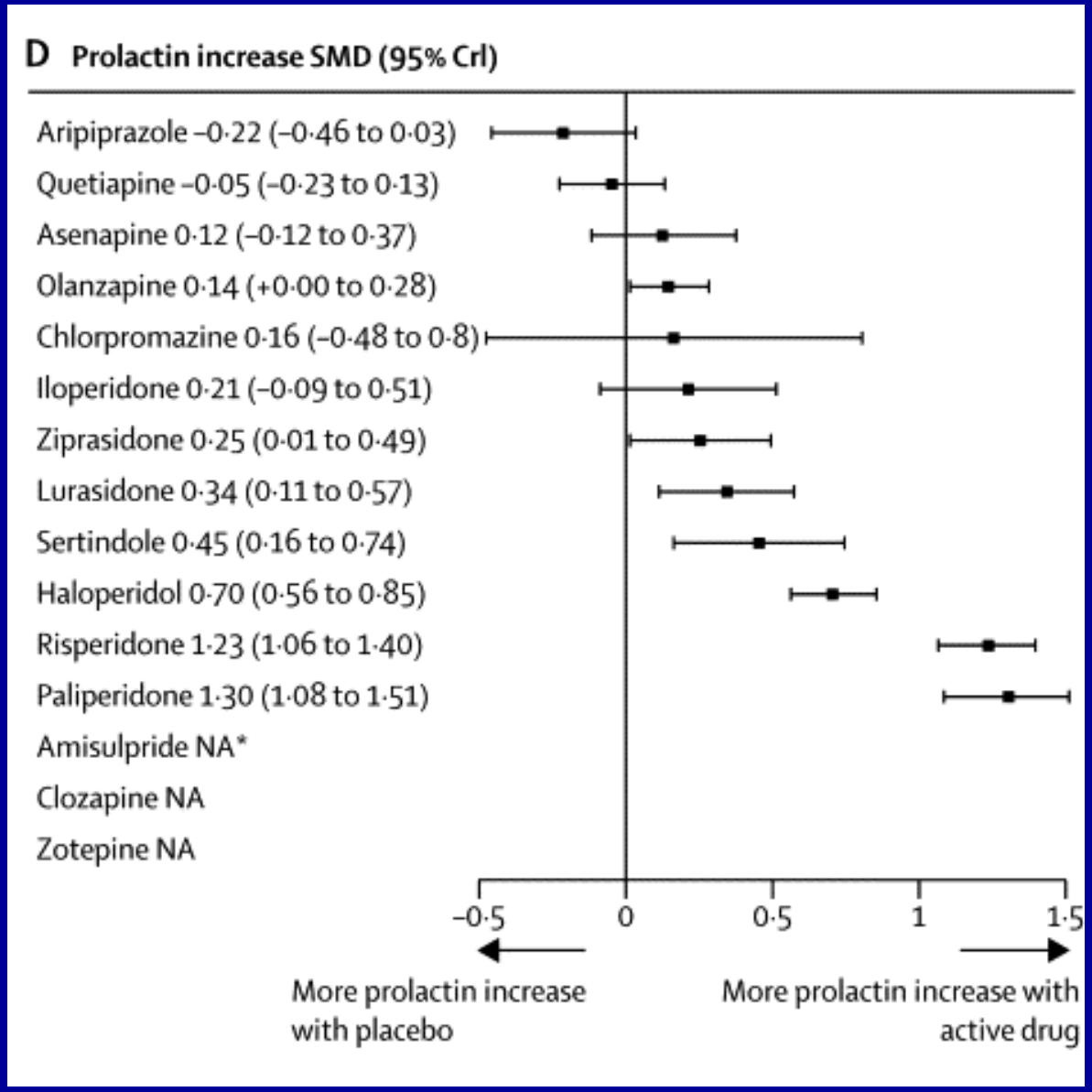
- First generation antipsychotics cause EPS, whereas second generation antipsychotics cause weight gain and metabolic adversities.



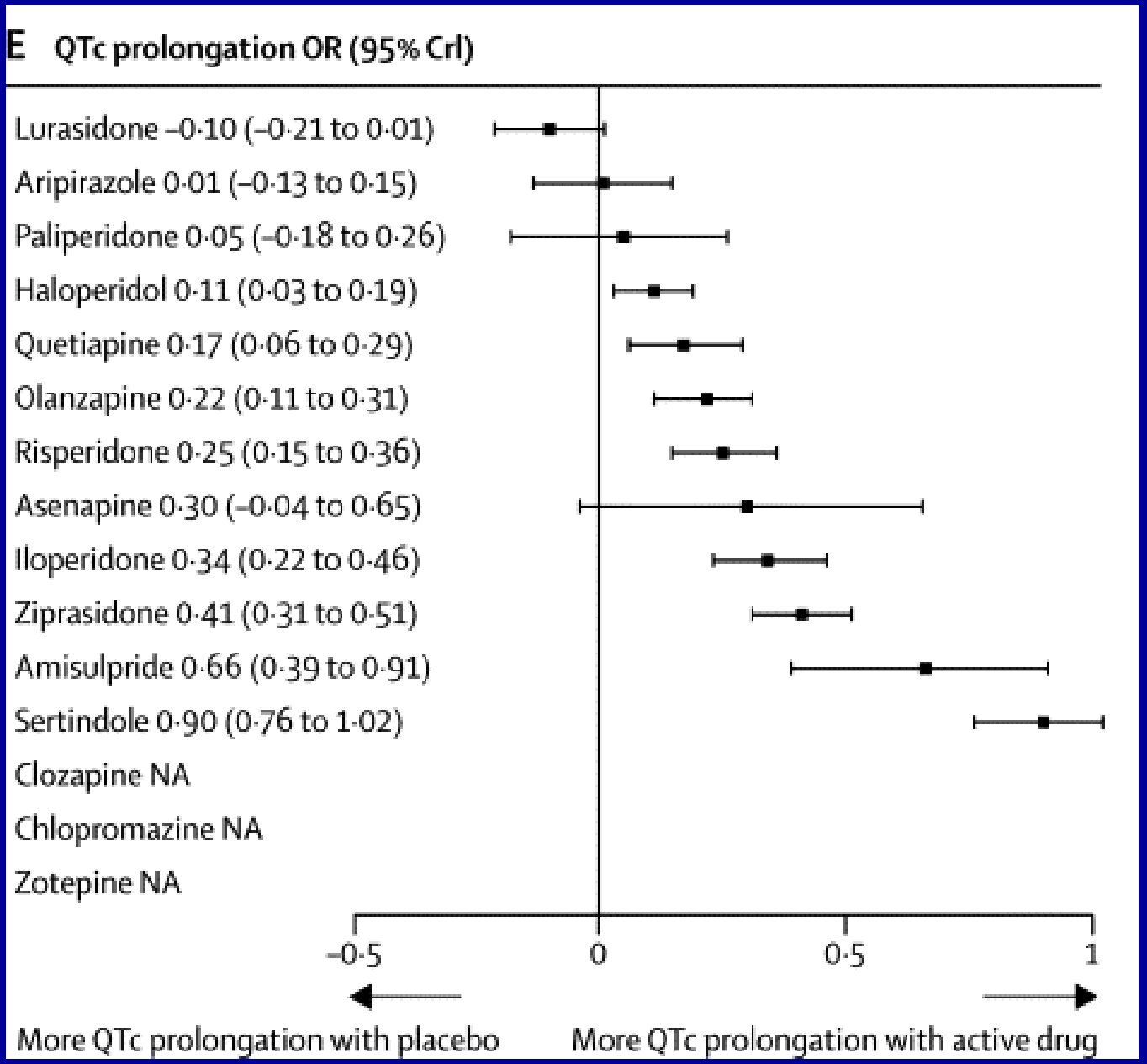
Leucht et al. Lancet 2013



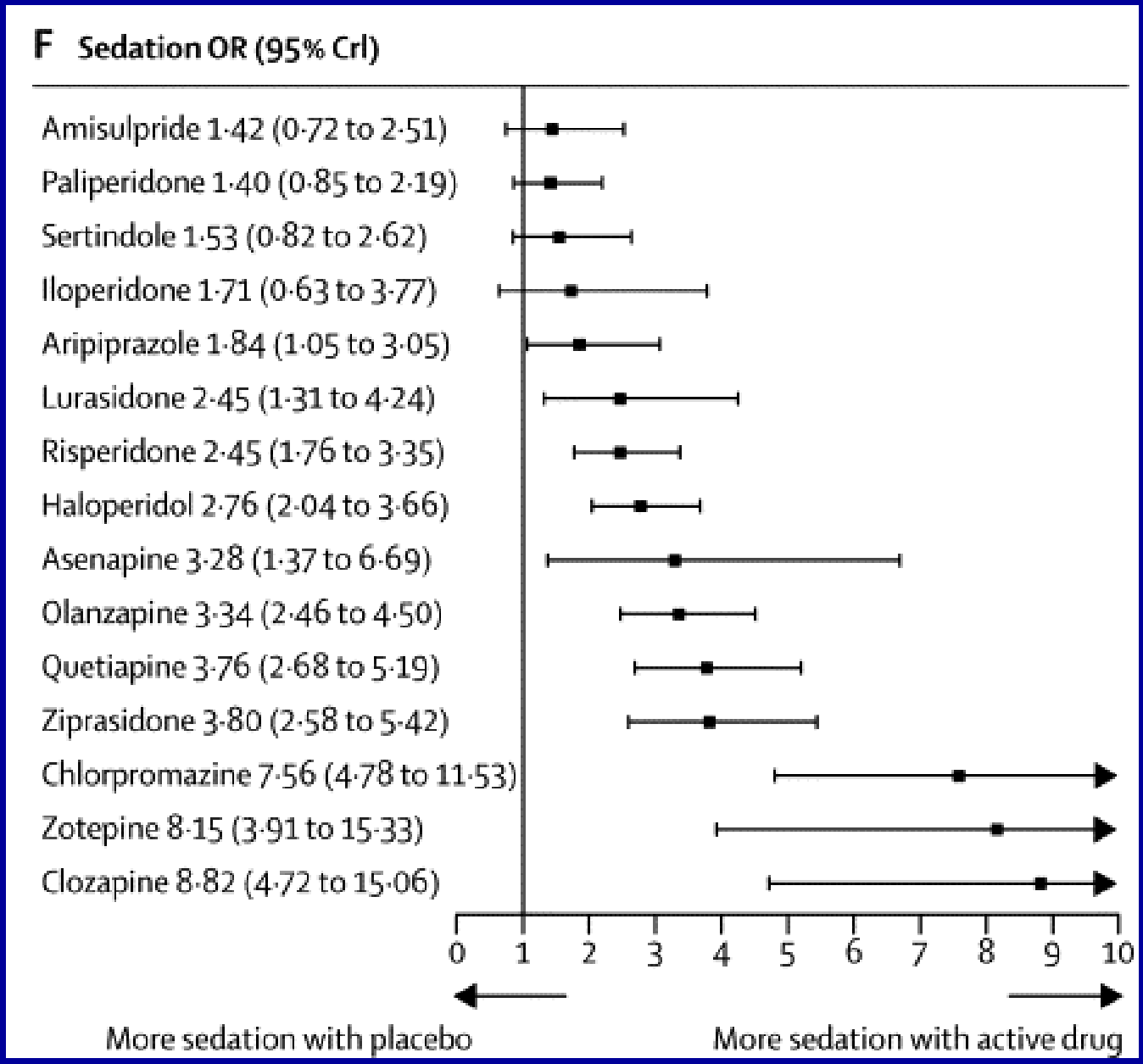
Leucht et al. Lancet 2013



Leucht et al. Lancet 2013



Leucht et al. Lancet 2013



Leucht et al. Lancet 2013

Controversy # 4

- Long-acting/ depot antipsychotics decrease relapse in psychosis compared to oral treatment

“Yeah but no but yeah but no.”

Vicky Pollard, Little Britain

- Kane JM et al. J Clin Epidemiol 2013;66(Suppl 8):S37-41; Kirson NY et al. J Clin Psychiatry 2013;74:568-75;
- Kishimoto T et al. Schizophr Bull 2014;40:192-213; Leucht C et al. Schizophr Res 2011;127:83-92.

Controversy # 5

- How well do RCTs of antipsychotic efficacy translate into usual clinical practice?

Systematic reviews of RCTs

- RCT
  - Advantage: «gold standard»
  - Limitations:
    - Short duration (80% ≤ 12 weeks)

      Leucht et al., 2009
    - Highly selected samples (→ 90% excluded)
    - Small samples (Most studies with N≈60)

      Leucht et al., 2008
    - Often sponsered by pharma industry

      Heres et al., 2006

Pragmatic/ naturalistic/ effectiveness studies

- Advantages:
  - More representative samples
  - Larger N
  - Longer duration
  - Independent (some)
- Disadvantages:
  - Methodologically less stringent
  - Heterogeneous samples
  - Sponsorship?

Examples

- CATIE
- CUtLASS
- EUFEST

BMC Psychiatry

BioMed Central

Research article

Open Access

Effectiveness of second generation antipsychotics: A systematic review of randomized trials

Erik Johnsen*[1] and Hugo A Jørgensen[1,2]

- Olanzapine longest time to all cause discontiuation (chronic schizophrenia)
- No consistent differences among SGAs for global or symptoms outcomes
- Olanzapine more weight gain and adverse impact on serum lipids

Johnsen&Jørgensen.BMC Psychiatry 2008;10:26

CUtLASS 1

Cost Utility of the Latest Drugs in Schizophrenia Study

- Quality of Life: FGA = SGA
- PANSS, CDSS, GAF, adherence: FGA = SGA
- Costs: FGA = SGA

Jones PB et al. Arch Gen Psychiatry 2006; 63:1079-87.

EUFEST

European First-Episode Schizophrenia Trial

- All cause discontiuation lower with SGAs compared to haloperidol

Kahn RS et al. Lancet 2008; 371:1085-97.

EUFEST - 1 year outcomes

Outcome	Halop	Amisu	Olanz	Queti	Zipra
≥ 50% response	37%	67%	67%	46%	56%
Remision	17%	40%	41%	24%	28%
PANSS	53.3	52.1	52.4	52.9	53.1
CGI	3.0	2.3	2.4	2.9	2.5
GAF	64.3	74.4	68.3	64.2	66.8
CDSS	1.9	1.8	1.8	1.9	1.9

Boter H et al. Schizophr Res 2009; 115:97-103; Kahn RS et al. Lancet 2008; 371:1085-97

Johnsen *et al. BMC Psychiatry* 2010, **10**:26
http://www.biomedcentral.com/1471-244X/10/26

RESEARCH ARTICLE Open Access

Effectiveness of second-generation antipsychotics: a naturalistic, randomized comparison of olanzapine, quetiapine, risperidone, and ziprasidone

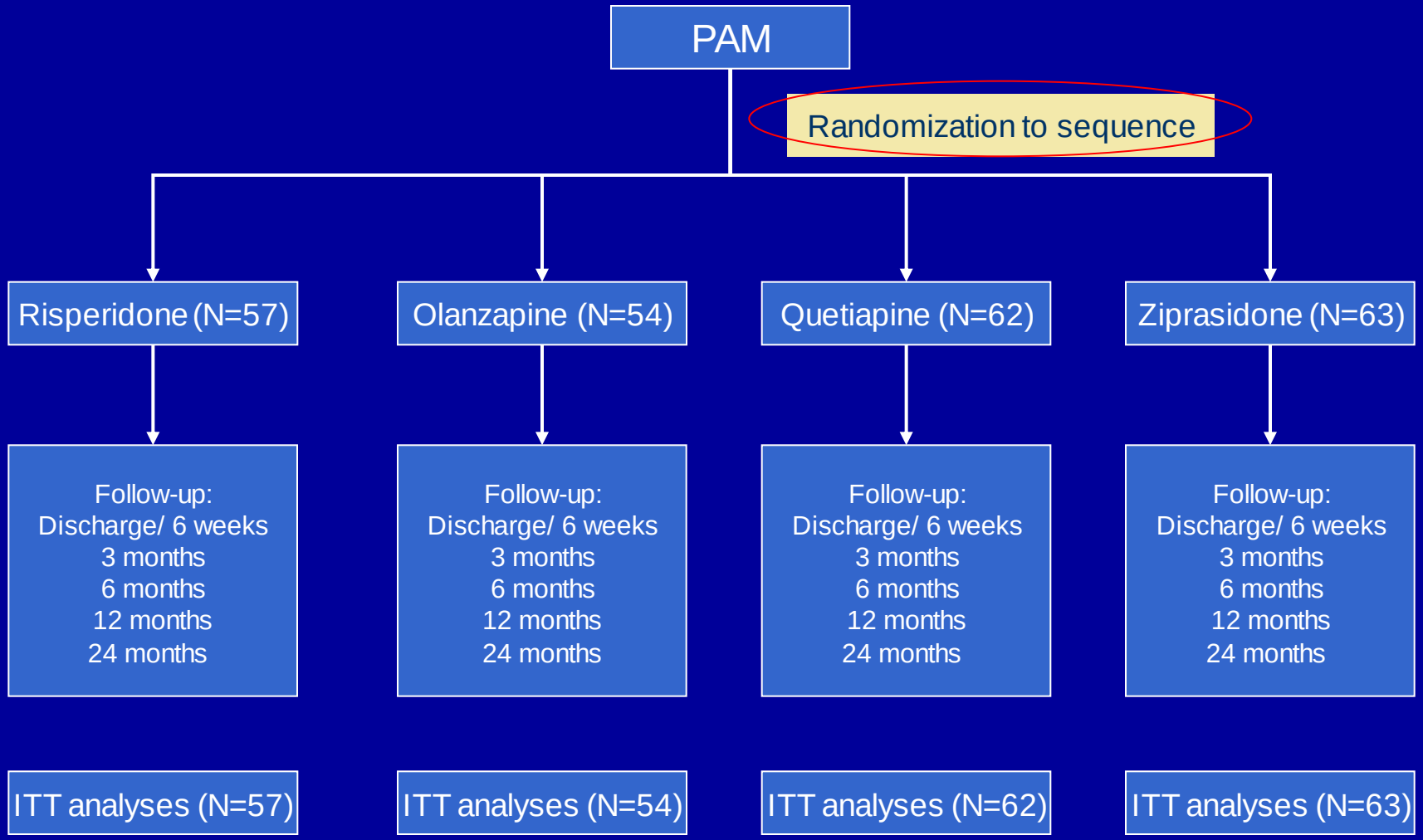
Erik Johnsen[1*], Rune A Kroken[1], Tore Wentzel-Larsen[2], Hugo A Jørgensen[1,3]

- The Bergen Psychosis Project
- Funding: Norwegian Research Council; Helse Vest; Helse Bergen

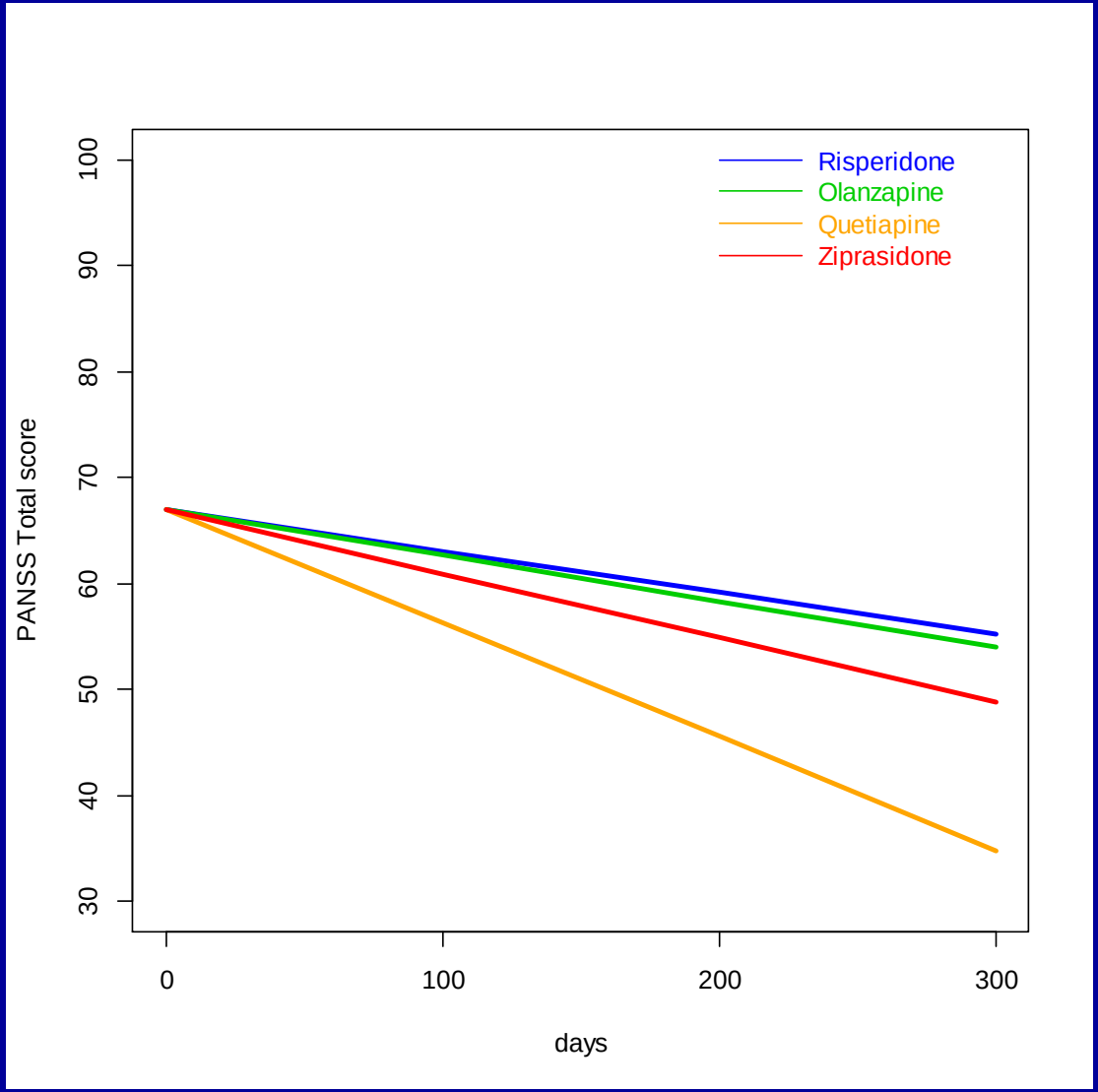
Inclusion criteria

- Adults acutely admitted with psychosis eligible for oral antipsychotic therapy

Design


PAM
Randomization to sequence
Risperidone (N=57)
Olanzapine (N=54)
Quetiapine (N=62)
Ziprasidone (N=63)
Follow-up:
Discharge/ 6 weeks
3 months
6 months
12 months
24 months
Follow-up:
Discharge/ 6 weeks
3 months
6 months
12 months
24 months
Follow-up:
Discharge/ 6 weeks
3 months
6 months
12 months
24 months
Follow-up:
Discharge/ 6 weeks
3 months
6 months
12 months
24 months
ITT analyses (N=57)
ITT analyses (N=54)
ITT analyses (N=62)
ITT analyses (N=63)

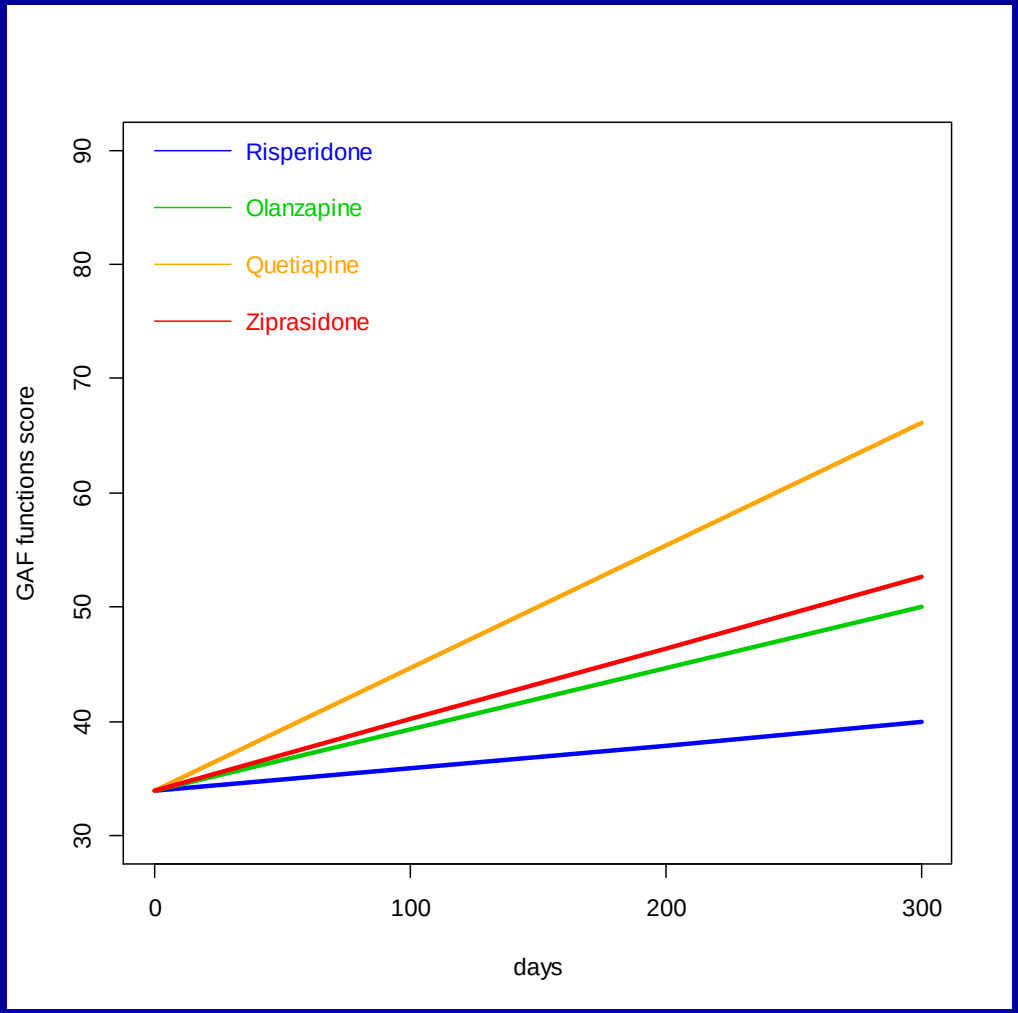
PANSS Total Score



Quetiapine > risperidone & olanzapine

Johnsen et al., BMC Psychiatry 2010;10:26

Global Assessment of Functioning - split version – functions scale

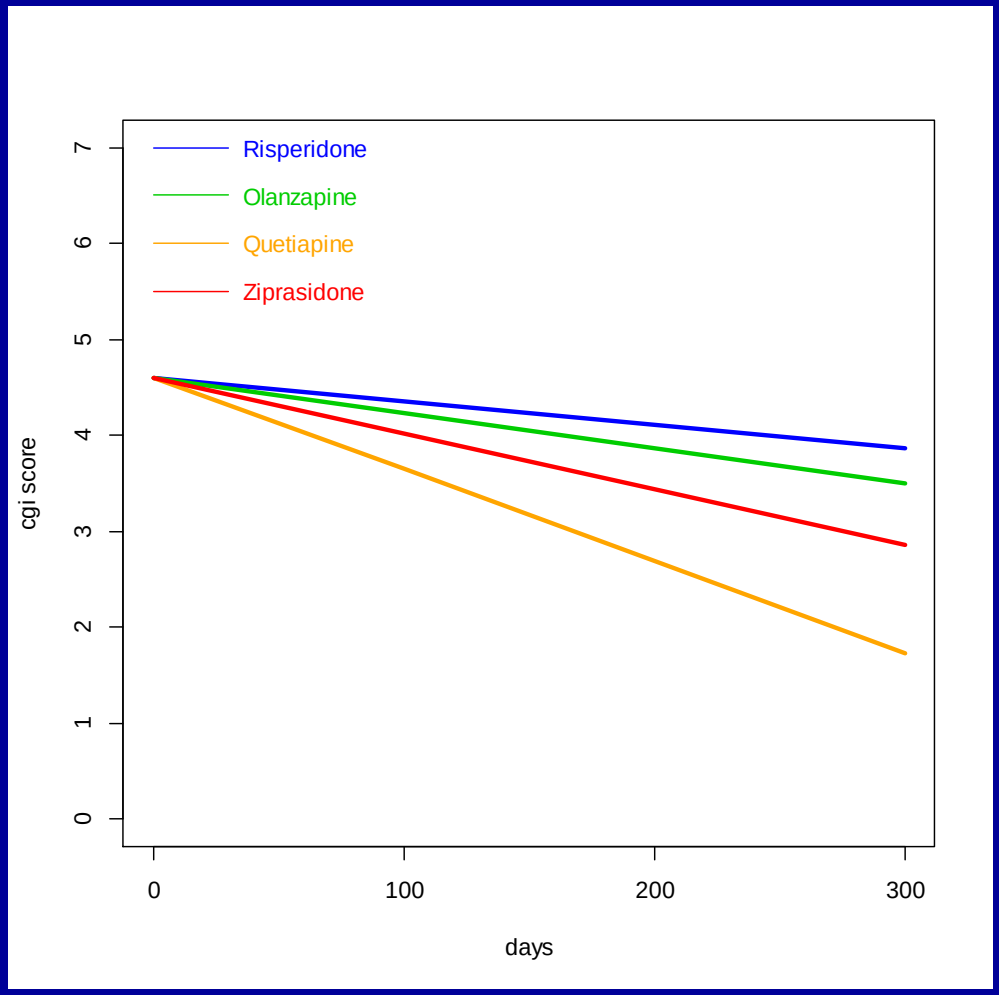


Quetiapine > risperidone & olanzapine & ziprasidone

Olanzapine > risperidone

Johnsen et al., BMC Psychiatry 2010;10:26

Clinical Global Impression – Severity of Illness score



Quetiapine > risperidone & olanzapine & ziprasidone

Johnsen et al., BMC Psychiatry 2010;10:26

Controversy # 6

- How well do RCTs of antipsychotic efficacy and pragmatic studies of effectiveness translate into usual clinical practice?

"It is not currently possible to prospectively predict which antipsychotic medication might be optimal for a given patient. Decisions about antipsychotic therapy consequently entail a trial and error process with careful monitoring of clinical response and adverse effects and an ongoing risk-benefit assessment."

World Psychiatric Association Pharmacopsychiatry Section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia
Tandon et al. Schizophr Res 2008;100:20-38.

Example – weight gain

- Treatment resistant schizophrenia, N=74 treated with clozapine (leponex)
- 6 weeks: +3.7kg (range -5.9 – 19.9 kg)
- 6 months: +7.3 kg (range -6.8 – 37.6 kg)

Meltzer et al. Schizophr Res 2002:19-27

Controversy # 7

- What can be gained by combining antipsychotics?

- Not evidence based (with a few possible exceptions)

Kroken&Johnsen, Curr Psychiatry Rep 2012;14:244-51

Controversy # 8

- What are the mechanisms of antipsychotic action?

Schizophrenia Bulletin vol. 35 no. 3 pp. 549–562, 2009
doi:10.1093/schbul/sbp006
Advance Access publication on March 26, 2009

The Dopamine Hypothesis of Schizophrenia: Version III—The Final Common Pathway

Oliver D. Howes[2,3] and Shitij Kapur[1,2]

	FGA			SGA					TGA
	Typical			Atypical					
Rec	Chlo	Halo	Amis	Cloz	Risp	Olan	Quet	Zipr	Arip
D1	+	++	-	++	+	++	+	+	+
D2	+++	++++	+++	+	+++	++	+	+++	++++
D3	+++	+++	+++	+	+++	++	+	+++	++++
D4	++	+++	-	++	+++	++	++	++	++
5HT1A	-	-	-	+	+	-	+	+++	+++
5HT2A	+++	++	-	++	++++	+++	++	++++	+++
5HT2C	++	-	-	++	++	++	-	++	+
α1	++++	+++	-	+++	++++	++	+++	++	++
α2	++	-	-	+	++	+	-	-	-
H1	++++	++	-	+++	++	+++	++	++	-
M1	++	-	-	+++	-	+++	+	-	-

Brain Research Bulletin 83 (2010) 108–121

Contents lists available at ScienceDirect

Brain Research Bulletin

journal homepage: www.elsevier.com/locate/brainresbull

Research report

N-methyl-D-aspartate (NMDA) receptor dysfunction or dysregulation: The final common pathway on the road to schizophrenia?

Joshua T. Kantrowitz, Daniel C. Javitt*

Schizophrenia Research Center, Nathan Kline Institute for Psychiatric Research/New York University School of Medicine, 140 Old Orangeburg Road, Orangeburg, NY 10962, United States

Progress in Neurobiology 93 (2011) 13–24

Contents lists available at ScienceDirect

Progress in Neurobiology

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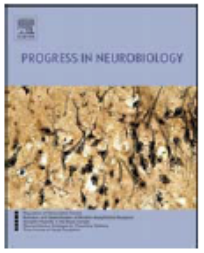
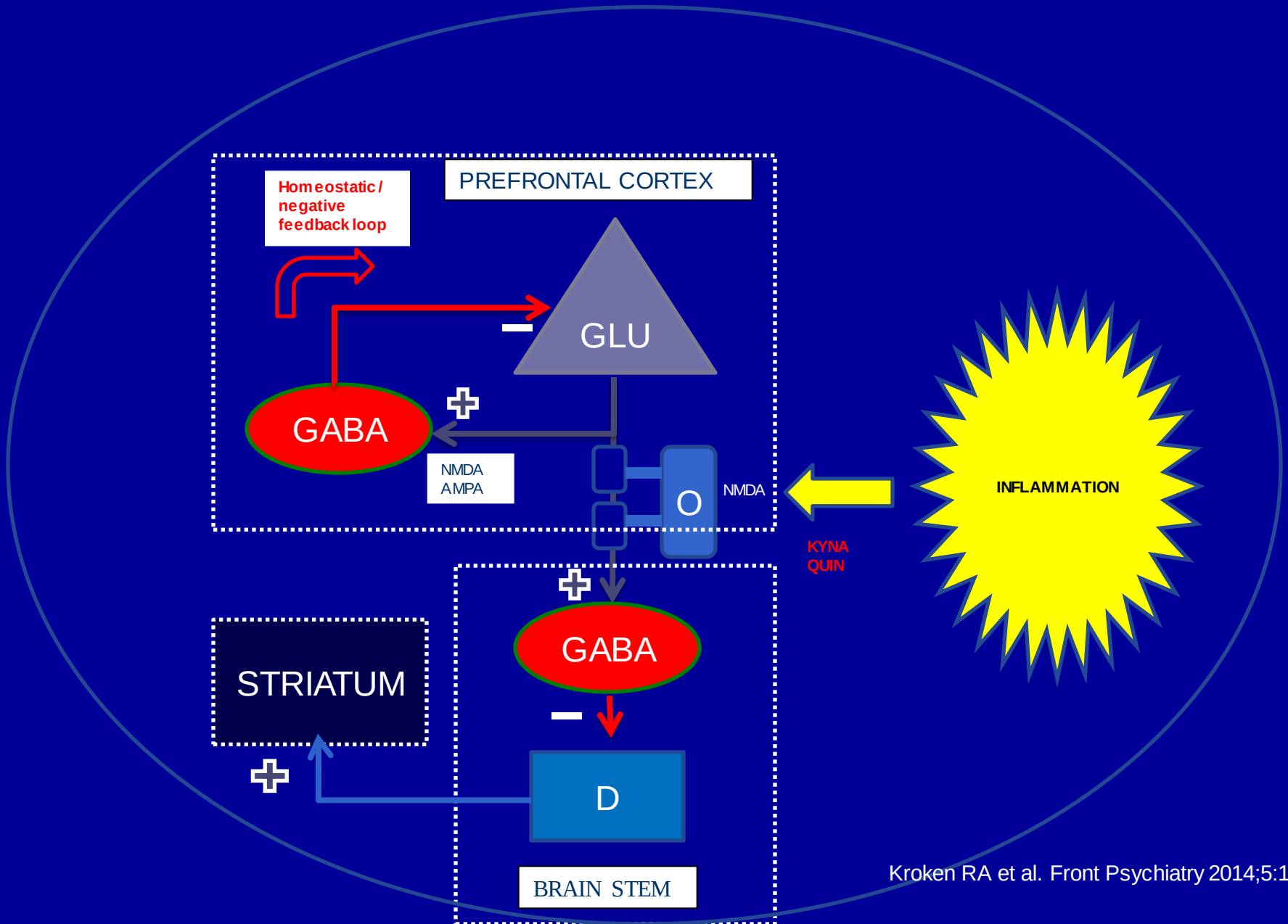


Linking oligodendrocyte and myelin dysfunction to neurocircuitry abnormalities in schizophrenia

Nagahide Takahashi, Takeshi Sakurai, Kenneth L. Davis, Joseph D. Buxbaum *

Conte Center for the Neuroscience of Mental Disorders and the Department of Psychiatry, Mount Sinai School of Medicine, New York, NY 10029, USA



Kroken RA et al. Front Psychiatry 2014;5:11.

Controversy # 9

- Do antipsychotics shrink the brain?

“Yeah but no but yeah but no.”

Vicky Pollard, Little Britain

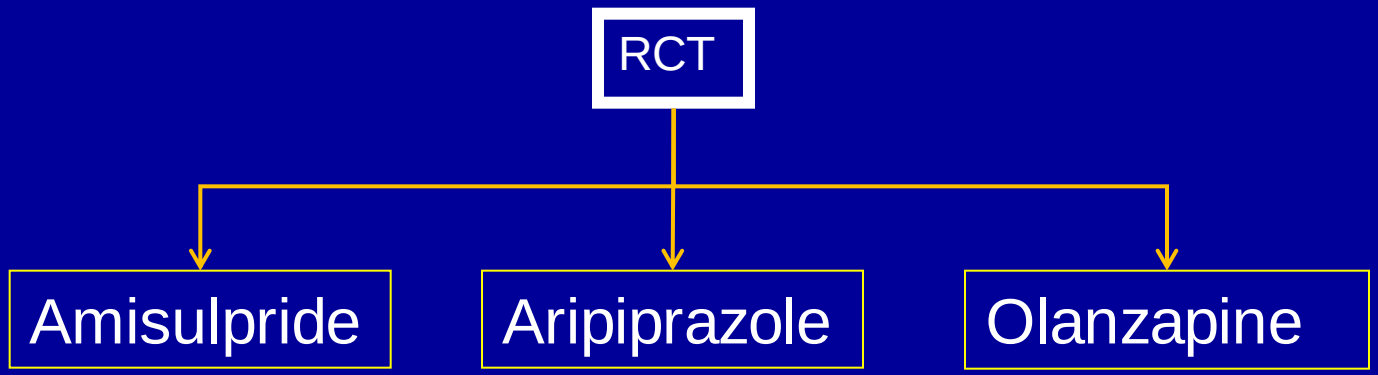
- Yang C et al. Psychopharmacology 2014;Epub ahead of print; Veijola J et al. PLoS One 2014;9:e101689; Goghari VM et al. Schizophr Res 2013;149:149-55; Fusar-Poli P et al. Neurosci Biobehav Rev 2013;37:1680-91; Andreasen NC et al. Am J Psychiatry 2013;170:609-15; Vita A et al. Transl Psychiatry 2012;2:e190; Mamah D et al. Front Psychiatry 2012;3:96; Ho BC et al. Arch Gen Psychiatry 2011;68:128-37.

Conclusions

- Antipsychotics have moderate to large effect sizes
- Differences among antipsychotics exist for effects, and to a larger extent, for side effects
- Effects and side effects are unpredictable in the individual patient
- Combination therapy is not evidence based
- Depot>oral probably in relapse prevention
- Neurotoxicity: Unresolved

Where do we go from here?

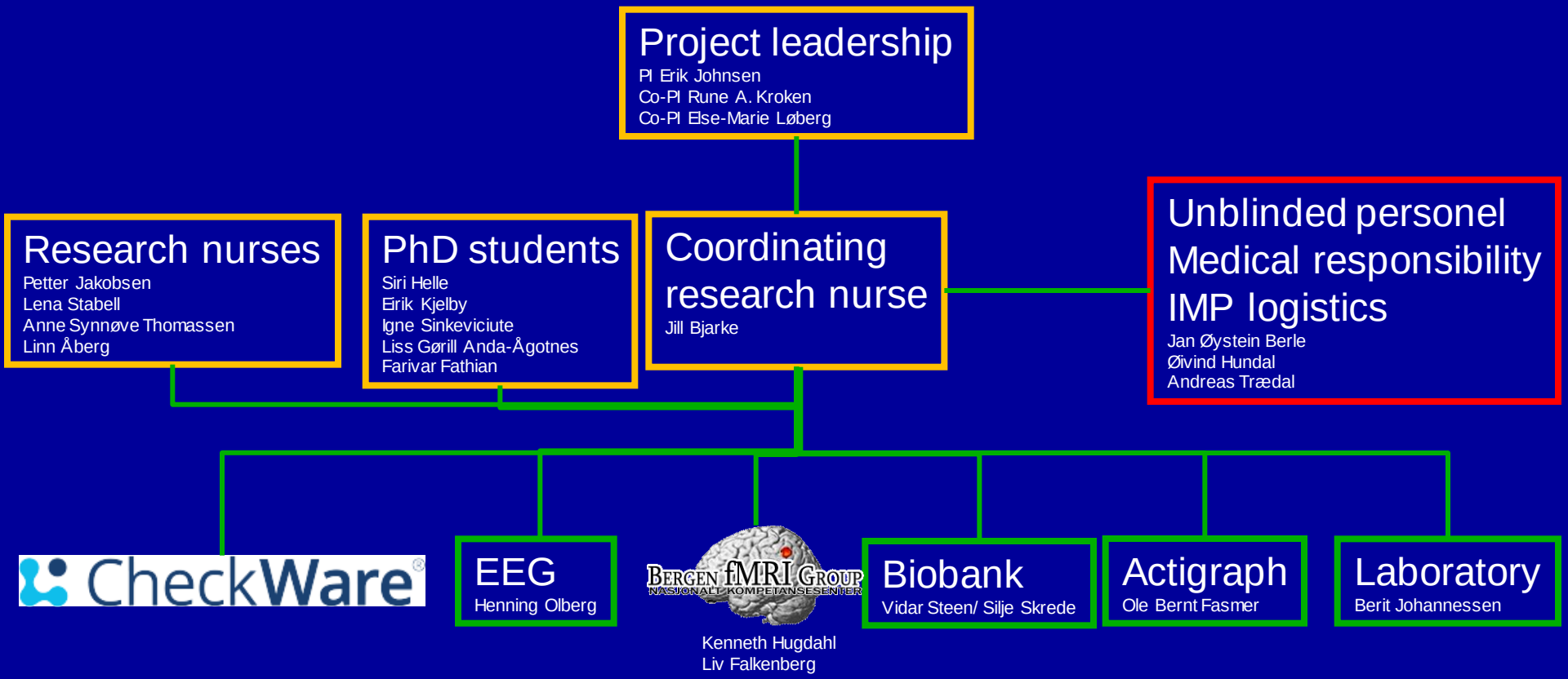
best intro



Rec	Amisulpride	Olanzapine	Aripiprazole
D1	-	++	+
D2	+++	++	++++
D3	+++	++	++++
D4	-	++	++
5HT1A	-	-	+++
5HT2A	-	+++	+++
5HT2C	-	++	+
α1	-	++	++
α2	-	+	-
H1	-	+++	-
M1	-	+++	-


eulast

Acknowledgements



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Thank you for your attention!