Safety and tolerability dei nuovi agonisti parziali: evidenze relative agli studi in add-on con clozapina

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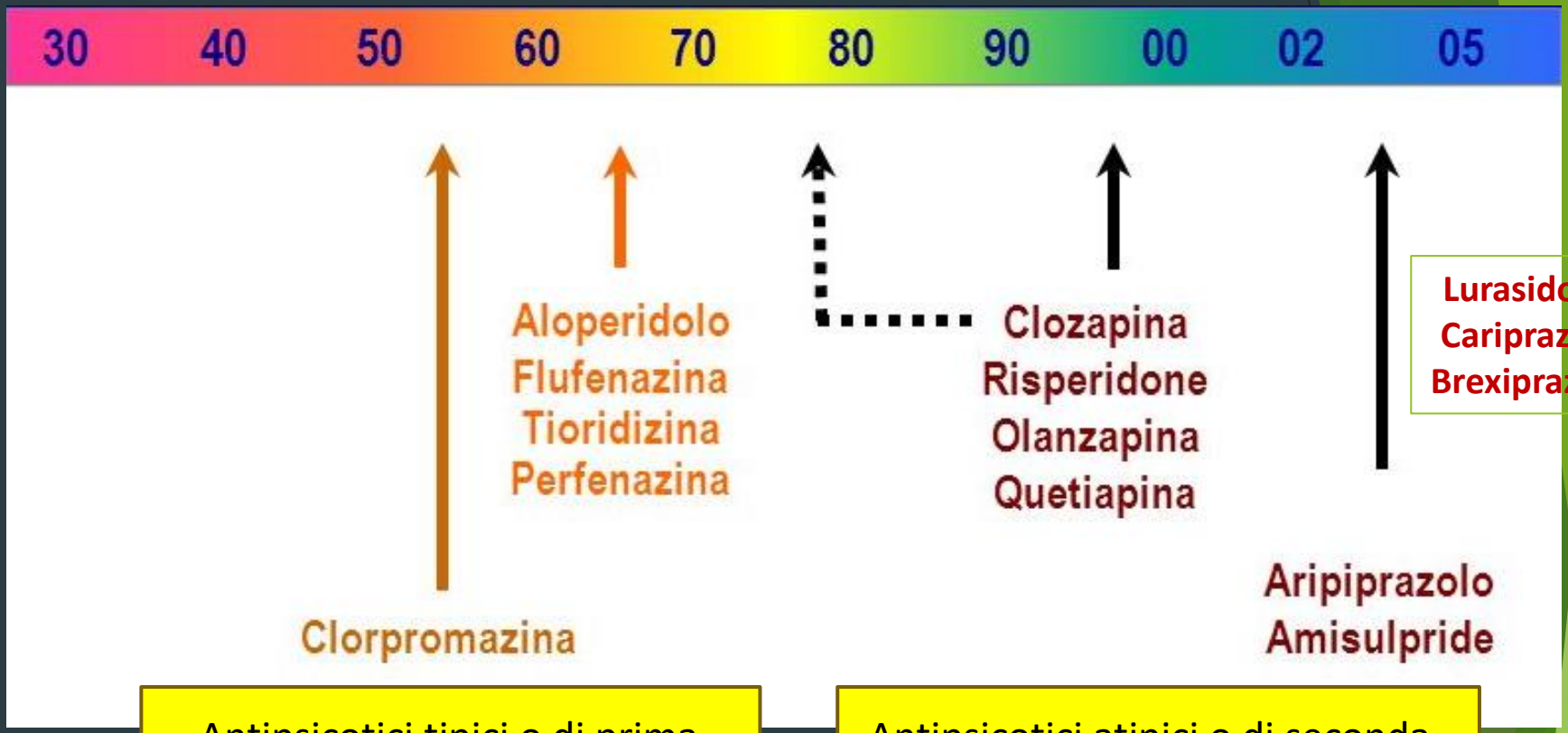
Evoluzione degli antipsicotici



Antipsicotici tipici o di prima generazione

Antipsicotici atipici o di seconda generazione

Il miglioramento della **qualità della vita** riferito dal paziente è risultato significativamente più alto nei pazienti schizofrenici trattati con **antipsicotici di seconda generazione** rispetto a quelli trattati con antipsicotici di prima generazione, quando la selezione del trattamento è stata individualizzata.

The lancet. Grunder et al. 2016.

Comparisong between APs efficacy

1. Newer APs are recommended as the treatment of choice, but older APs are less costly and are still used worldwide

2. A clear understanding of the relative risks and benefits is essential for decision making

3. Primary outcome as measured by rating scales;

4. Secondary outcomes, all-cause discontinuation (side effects, depression, quality of life, social functioning)

Individual effect size estimates suggest that all APs reduced overall symptoms more than placebo.

However, overlapping between APs suggest that differences between most individual drugs were not significant.

With few exceptions, **only clozapine, amisulpride, zotepine, olanzapine, and risperidone** were significantly more efficacious than other APs

Huhn et al. ***Lancet*** 2019

Superior Efficacy of Clozapine

1. CATIE Study: Effectiveness
2. CUtLASS 2: Efficacy in treatment resistant schizophrenia
3. Cochrane 2000; 2009
4. Meta-analyses; systematic review

Disadvantages

- Side effect profile
- Drug underutilized

Acta Psychiatr Scand 2018: 138: 281–288

DOI: 10.1111/acps.12954

ACTA PSYCHIATRICA SCANDINAVICA

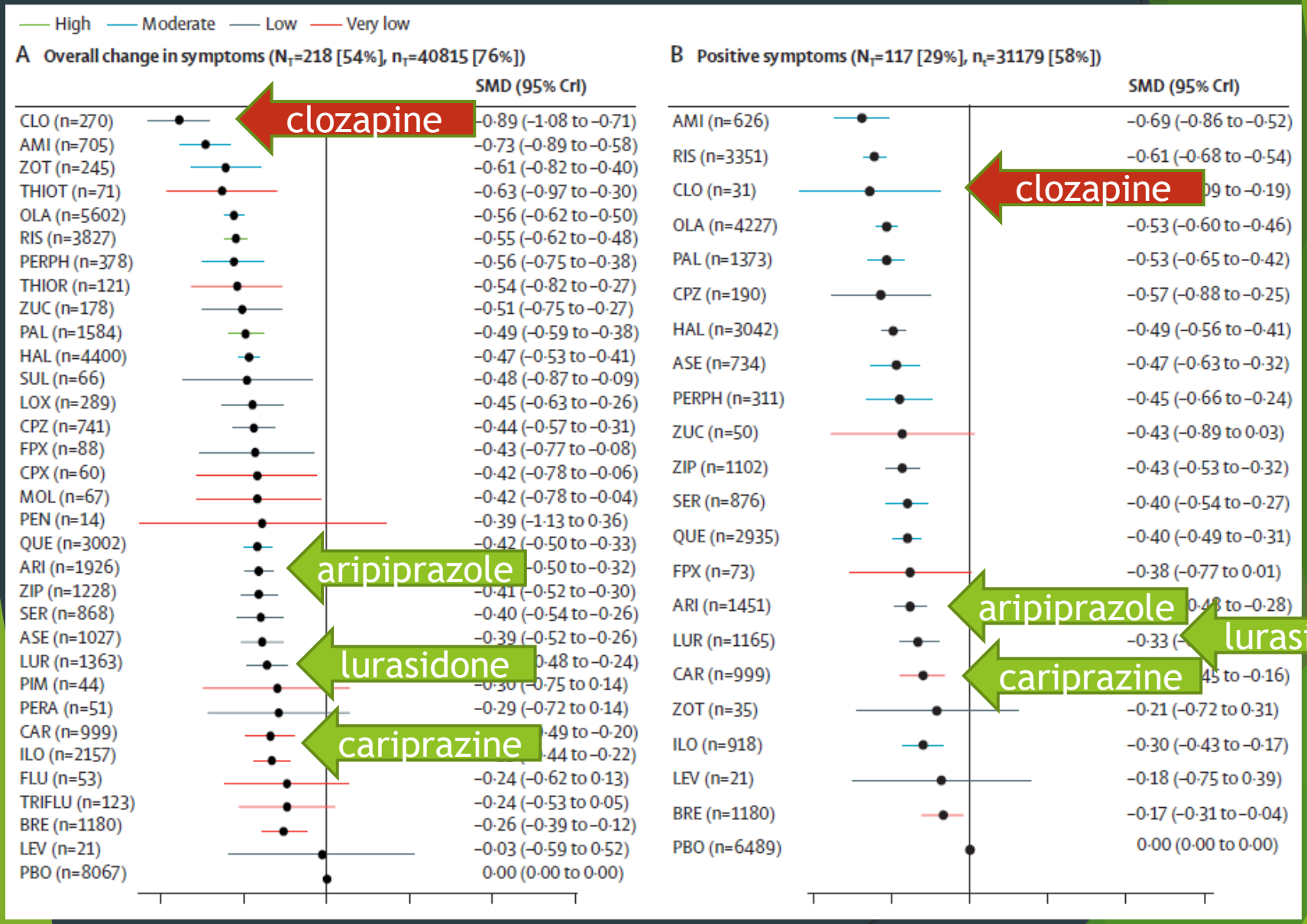
Systematic Review-Meta-analysis

Clozapine as a first- or second-line treatment in schizophrenia: a systematic review and meta-analysis

Okhuijsen-Pfeifer C et al

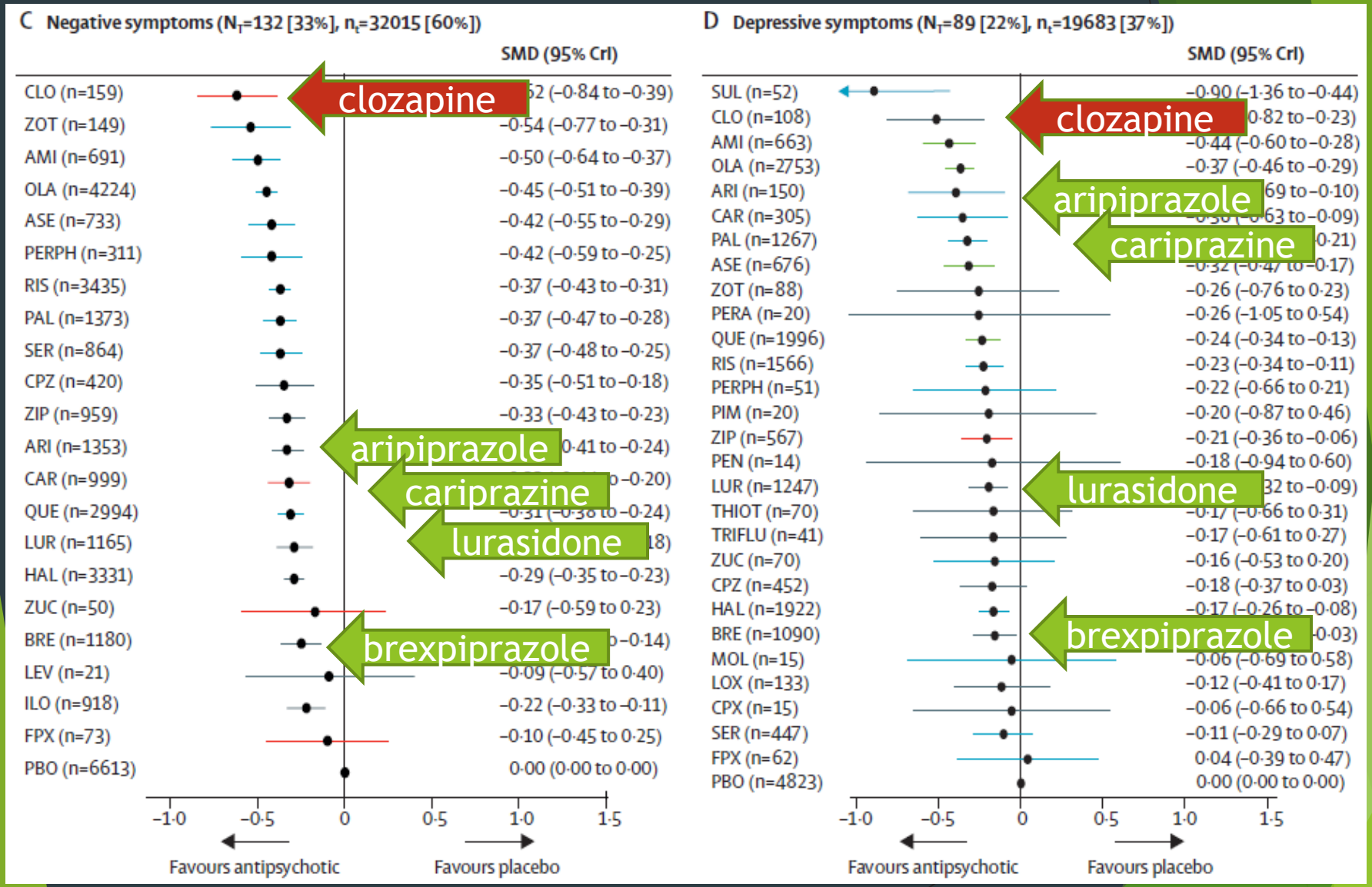
- Clozapine as first line treatment effective as other APs (50%) or more effective (50%)
- Sensitivity meta-analysis showed clozapine as more effective than risperidone as first line treatment
- Clozapine as second line treatment more effective than other APs
- Sensitivity meta-analysys didn’t show a increased efficacy compared to other APs

Efficacy on **overall** and **positive** symptoms



Huhn et al. ***Lancet*** 2019

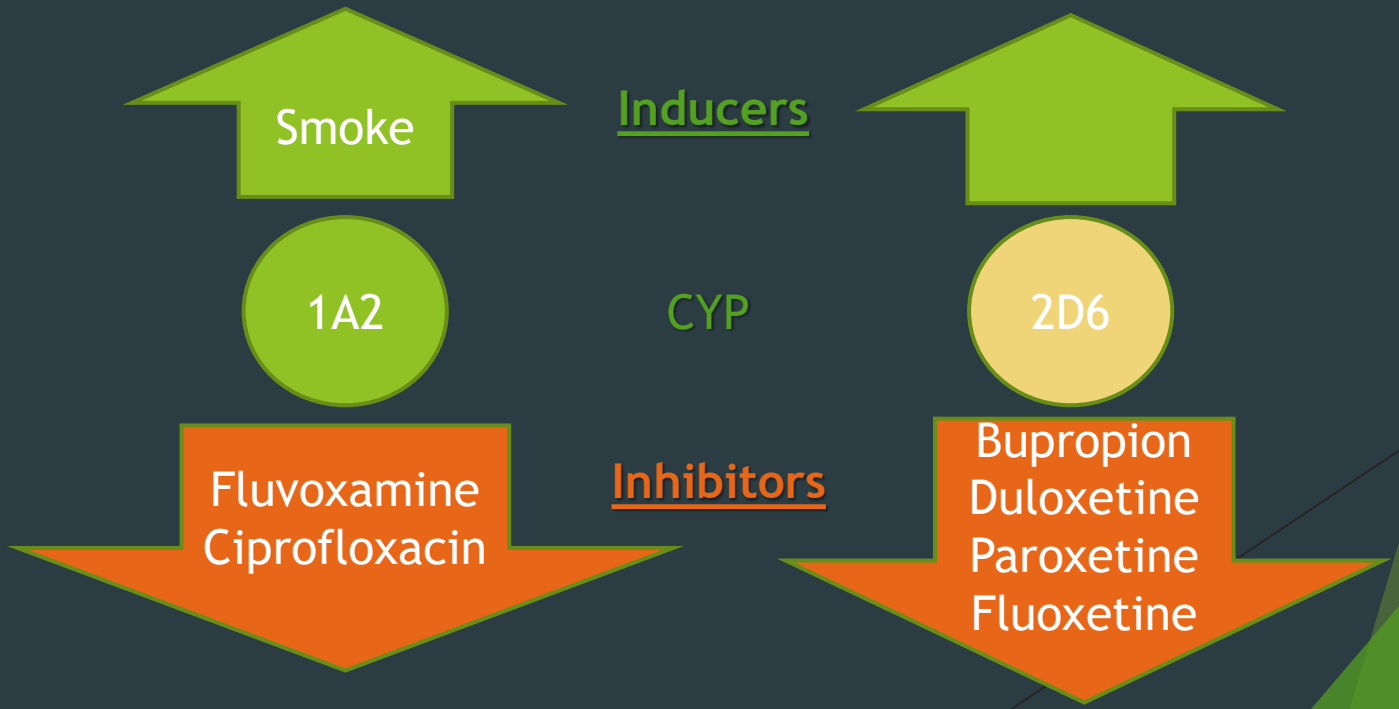
Efficacy on **negative** and **depressive** symptoms



Huhn et al. ***Lancet*** 2019

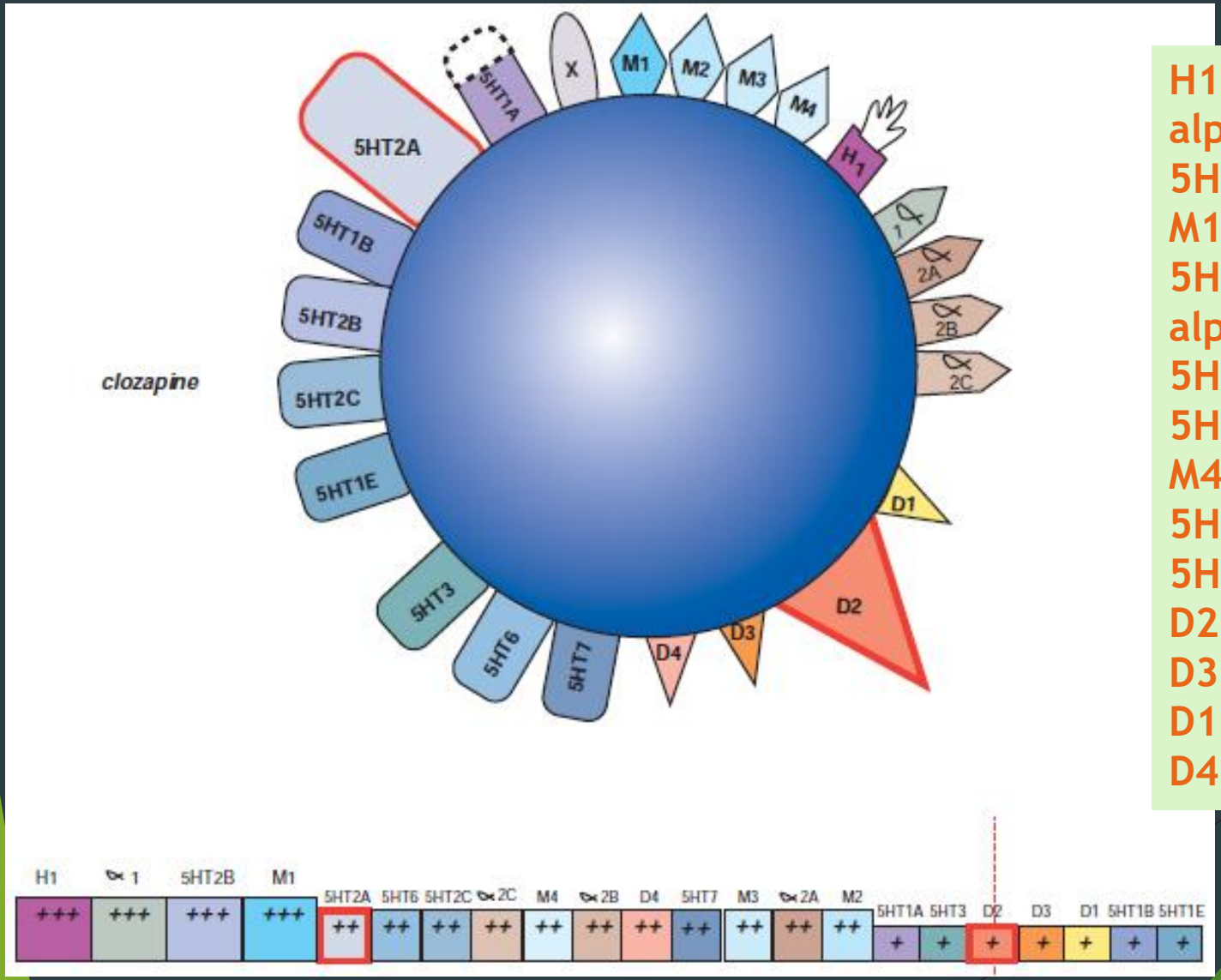
Clozapine pharmacokinetics

- Half life 5-16 hours
- Metabolized mostly by CYP450 1A2 and lesser by 2D6 and 3A4
- Inhibits itself CYP450 2D6
- CYP inducers decrease clozapine blood level, while inhibitors increase it



Stahl's essential psychopharmacology (2013)

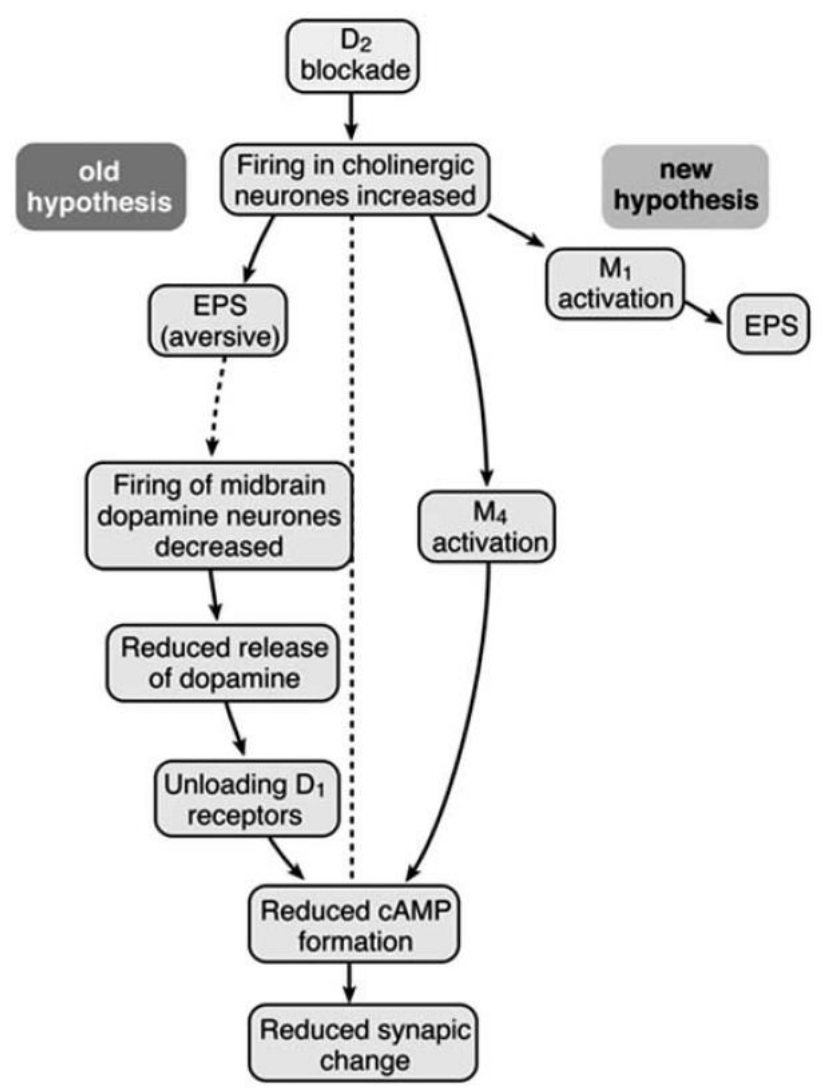
Clozapine



H1 antagonist
alpha1 antagonist
5HT2B antagonist
M1 partial agonist
5HT2A antagonist
alpha2 antagonist
5HT6 antagonist
5HT2C antagonist
M4 partial agonist
5HT7 antagonist
5HT1A partial agonist
D2 antagonist
D3 antagonist
D1 antagonist
D4 antagonist

Stahl's essential psychopharmacology (2013)

Hypothesis for efficacy of clozapine and its metabolite N-desmethilclozapine



- Rapid dissociation from D2 receptors (like quetiapine)
- High 5HT2A/D2 affinity ratio (like other APs)
- High D4/D2 affinity ratio (like asenapine and ziprasidone)
- α1 antagonism (like prazosin)
- α2 antagonism (like guanfacine)
- M1 agonism (like olanzapine)
- H1 and H2 inverse agonism

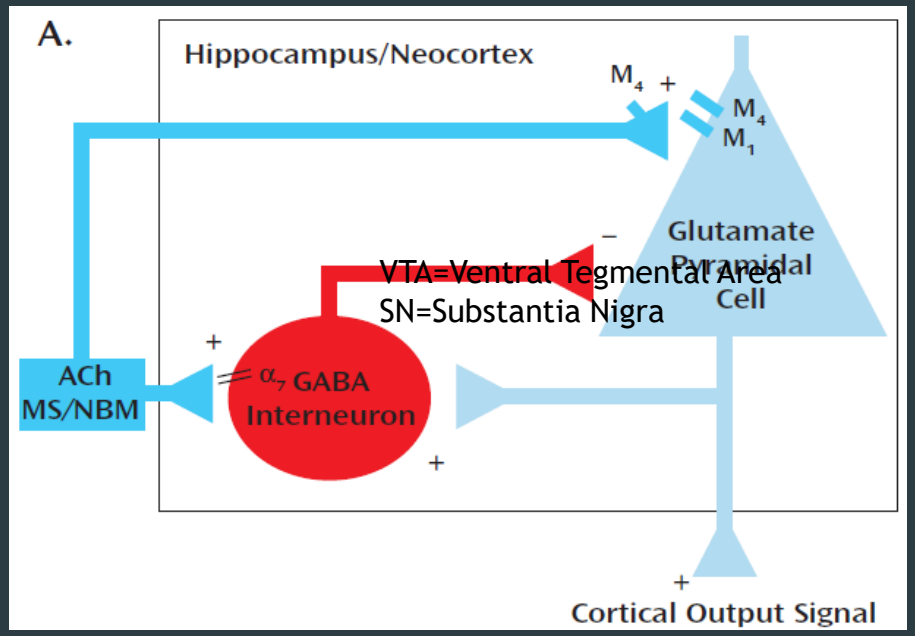
Clozapine is also a M4 partial agonist

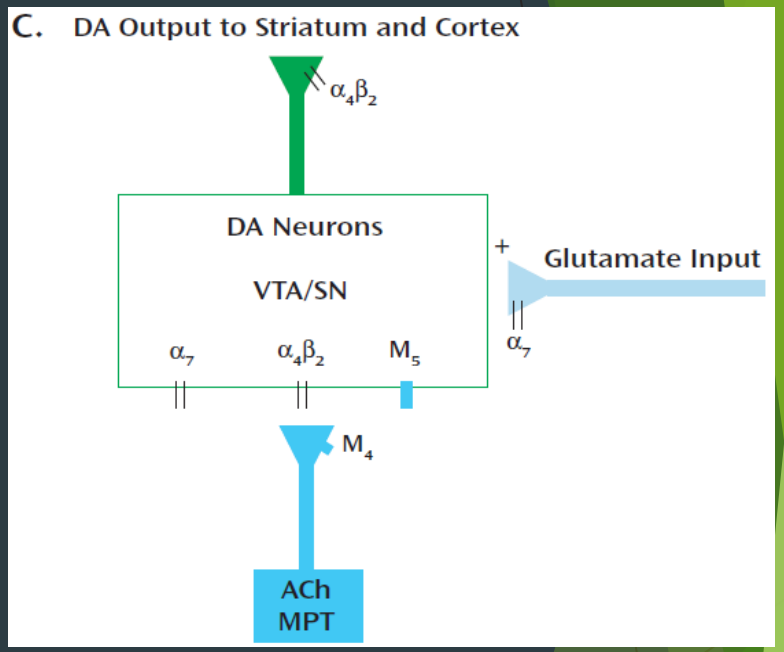
Nucifora FC et al, Neurother (2017)

Miller R, Current Neuropharm (2009)

Agonist Cholinergic pathways in psychosis

Dopaminergic pathways from VTA to striatum and cortex are also mediated by muscarinic receptors M1 and M4





MS=Medial Septum
NBM=Nucleus basalis of Meynert

MPT=Mesopontine Tegmentum

Neocortex and hippocampus receive cholinergic input. Modulation by M4 receptors in glutammate pyramidal cells from hippocampus to cortex

Modulation by M4 receptors in DA pathways from VTA to striatum and cortex

Clozapine: a M4 partial agonist

- Classical neuroleptic drugs disinhibit striatal cholinergic interneurones and increase acetyl choline release. Their effects may then depend on stimulation of muscarinic receptors on principle striatal neurones (M4 receptors, with reduction of cAMP formation, for therapeutic effects; M1 receptors for motor side effects).
- Refractoriness or low sensitivity to antipsychotic effects could then arise from low density of cholinergic interneurones.
- Clozapine probably owes its special actions to direct stimulation of M4 receptors. Clozapine is also a M4 partial agonist (higher affinity M4 than D2)
- Clozapine may act on the decreased number of intra-striatal cholinergic interneurons (for cytotoxic processes)

M4 stimulation

↓*in cAMP formation*

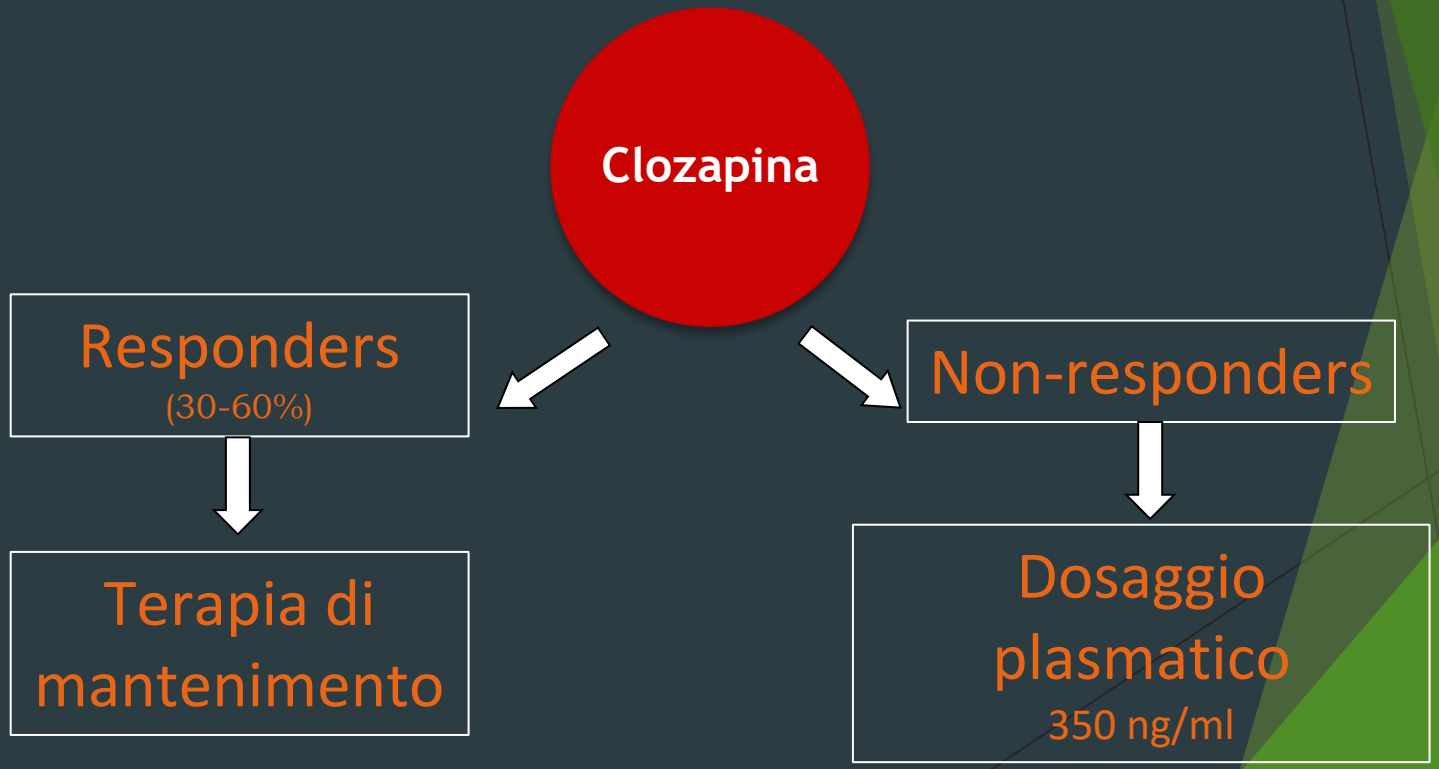
↓*DA-mediated synaptic potentiation*

↓*reinforcement processes in striatal-mesolimbic pathways*

reduction in diskinesia and psychosis

Efficacia clinica della Clozapina nella Schizofrenia

Studi prospettici, attestano l'efficacia clinica della Clozapina nel **30-61%** dei pazienti schizofrenici resistenti



Iqbal et al, *Ann Clin Psychiatry 2003; 15: 33-48* ; Llorca et *J Psychiatr Neurosci 2002; 27: 30-7;* Rostami-Hodjegan et al *J Clin Psychopharmacol 2004; 24: 70-8*

Clozapine efficacy on suicidality

- 50% of people with schizophrenia attempt suicide and 10% die for suicide
- Clozapine reduces suicidality more than olanzapine
- Reduction in suicidality from 28% to 3% in subjects treated with clozapine
- Discontinuation of clozapine may result in increasing suicidality (from 3% to 18%)
- Clozapine was more effective than quetiapine in reducing depressive symptoms (CATIE study)
- **Clozapine's ability to enhance periferical NE may be one of the mechanisms for suicidal reduction toghether with its ability to reduce substances use**

Khokhar JY et al, 2018

Pharmacological Treatment Algorithm for Schizophrenia (TMAP 99)

Atypical (Risperidone, Olanzapine or Quetiapine)

4 - 8 week trial

↓

If inadequate response, switch to a different atypical for additional 4-8 weeks

↓

If inadequate response, switch to long acting typical agent (e.g., haloperidol decanoate) **Monitor blood level**

↓

If inadequate response, switch to Clozapine

Titrate up to plasma level > 450 ng/ml as tolerated over 4 weeks

How and when to use clozapine

	Slow	Fast	Ultra-fast
Initial dose	12.5 mg	12.5 mg	25 mg
Phase I	25 mg increments every 2-3 days until reaching 100 mg/day	25 mg increments every day until reaching 100 mg/day	25-50 mg as needed every 6h in the first 24h.
Phase II	25 mg increment every day until reaching target dose	50 mg increments every day until reaching target dose	On subsequent days increase dose by no more than 100 mg/day until symptom control
Target dose	300-450 mg/day	300-450 mg/day	300-450 mg/day

Rubio and Kane, Acta Psychiatrica Scandinavica 2019 [Epub ahead of print]

Cochrane Library

Cochrane Database of Systematic Reviews

2017

Clozapine combined with different antipsychotic drugs for treatment-resistant schizophrenia (Review)

Barber S, Olotu U, Corsi M, Cipriani A

Quindici strategie di Augmentation, con Antipsicotici, Lamotrigina e SSRI

When Symptoms Persist: Clozapine Augmentation Strategies

by Peter Buckley, Alexander Miller, Jerry Olsen, David Garver, Del D. Miller, and John Csernansky

- Loxapine 25-200mg + clozapine 821mg → high efficacy
- Sulpiride 600mg + clozapine 400mg → low efficacy and increse in prolactinemia
- Pimozide 4mg + clozapine 425mg → some efficacy but no data on side effects
- Risperidone 3.8mg + clozapine 479mg → some efficacy and less sedation but akatisia and hypersalivation
- D-serine 30mg (agonist on NMDA glycine site but no BBB penetration) + clozapine 400-1200mg → no effect or worsening psychosis, good tollerability;
- Lithium: schizoaffective Pts; > asterixis; leukocite count

Schizophrenia Bull (2001)

Dosages of clozapine combinations

- clozapine 418mg + aripiprazole 8.7mg **vs**
  clozapine 413mg + haloperidol 2.1mg
- clozapine 550mg + amisulpride 437-600mg **vs**
  clozapine 537mg + quetiapine 595-900mg
- clozapine <=400mg + risperidone 4-6mg **vs**
  clozapine <=400mg + sulpiride 800-1200mg
- clozapine 437-450mg + risperidone 3.82mg **vs**
  clozapine 370-325mg + ziprasidone 134mg
- clozapine 479mg + ziprasidone 120-160mg **vs**
  clozapine 481mg vs quetiapine 400-750mg

Barber S et al, Cochrane Database 2017

Conclusions on combination with clozapine in TRS

Combination with

- **aripiprazole showed a better tollerability at 6 months than haloperidol**
- amisulpride showed a stronger efficacy than quetiapine
- risperidone showed a larger benefit on positive symptoms than sulpiride
- ziprasidone showed a strongest PANSS reduction than quetiapine

- **Combination treatment may allow to reduce its dosage resulting in lower side effects**

A few studied compared different combinations

no meta-analysis was possible to be performed

Barber S et al, Cochrane Database of Systematic Reviews 2017

Antidepressants and mood stabilizers add-on in TRS

Antidepressants (Total)	9		
Fluoxetine	5	296	−0.73 [−0.97, −0.50]*
Paroxetine	1	66	−0.97 [−1.48, −0.45]*
Duloxetine	1	33	−1.23 [−1.98, −0.48]*
Mirtazepine	2	35	−2.61 [−8.66, 3.44]
Antidepressants (Positive)	9		
Fluoxetine	5	269	−0.70 [−1.31, −0.09]*
Paroxetine	1	66	−0.51 [−1.00, −0.02]*
Duloxetine	1	33	0.00 [−0.68, 0.68]
Mirtazepine	2	35	−0.01 [−1.10, 1.09]
Antidepressants (Negative)	9		
Fluo			]*
Paro			]*
Dul			]*
Mirt			
Mood			
Sodi			]*
Lithium	1	59	−2.13 [−2.78, −1.49]*
Topiramate	1	43	−0.49 [−1.11, 0.12]
Lamotrigine	2	85	−0.33 [−2.26, 1.60]
Mood Stabiliser (Positive)	7		
Sodium Valproate	2	118	−1.54 [−1.96, −1.13]*
Lithium	1	59	−0.52 [−1.04, −0.00]*
Topiramate	1	43	−0.83 [−1.46, −0.20]*
Lamotrigine	2	85	−0.55 [−1.64, 0.53]
Mood Stabiliser (Negative)	7		
Sodium Valproate	2	118	−0.32 [−1.09, 0.45]
Lithium	1	59	−0.05 [−0.57, 0.46]
Topiramate	1	43	−0.87 [−1.50, −0.24]*
Lamotrigine	2	85	−0.63 [−2.29, 1.02]

MOST EFFECTIVE AUGMENTATION WAS FLUOXETINE (inhibition of CYP 2D6) (for negative symptoms)
AND SODIUM VALPROATE (in Bipolar Pts)

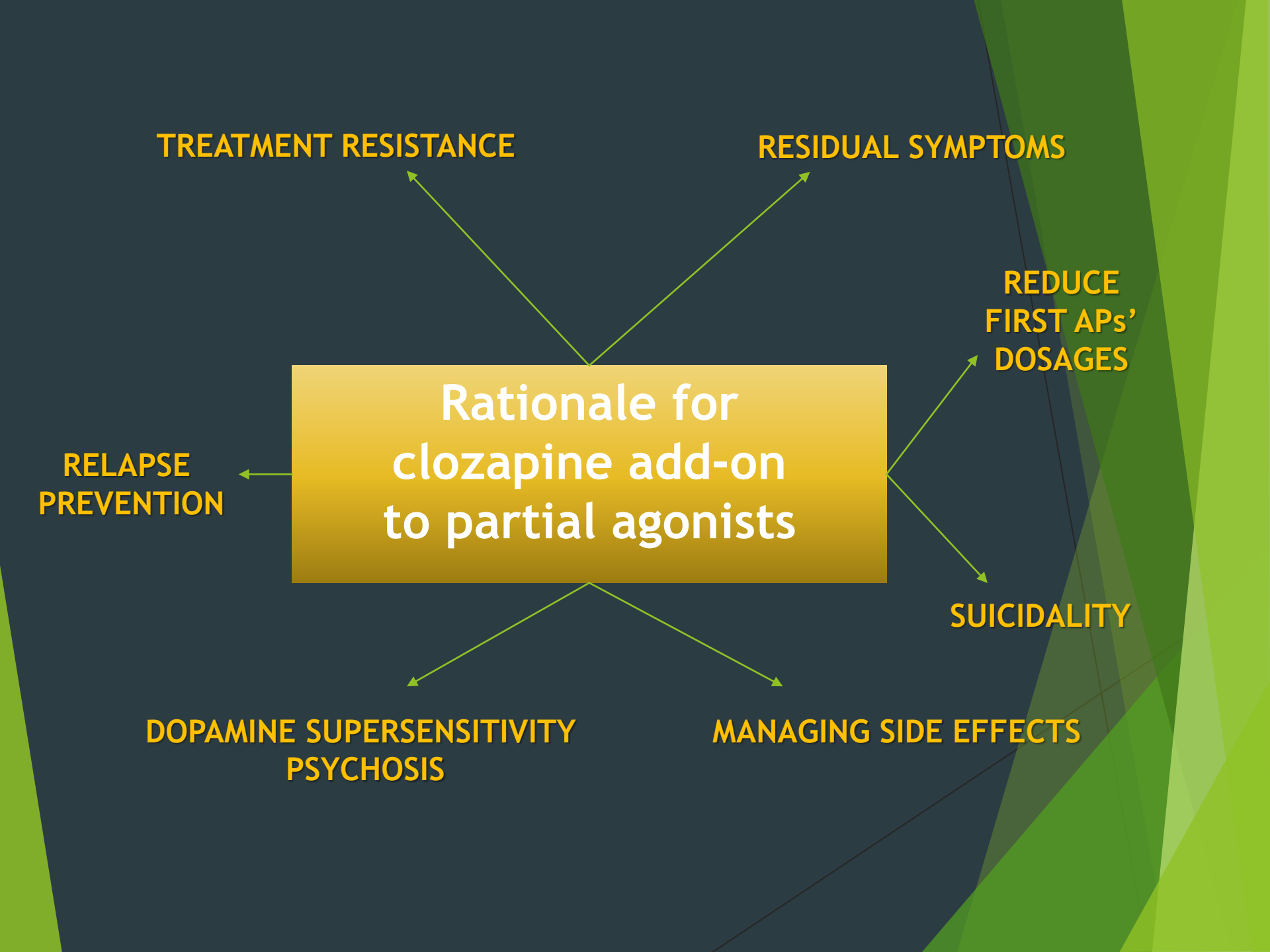
Siskind DJ et al, Aust NZJ Psy (2018)

Other add-on strategies to clozapine in TRS

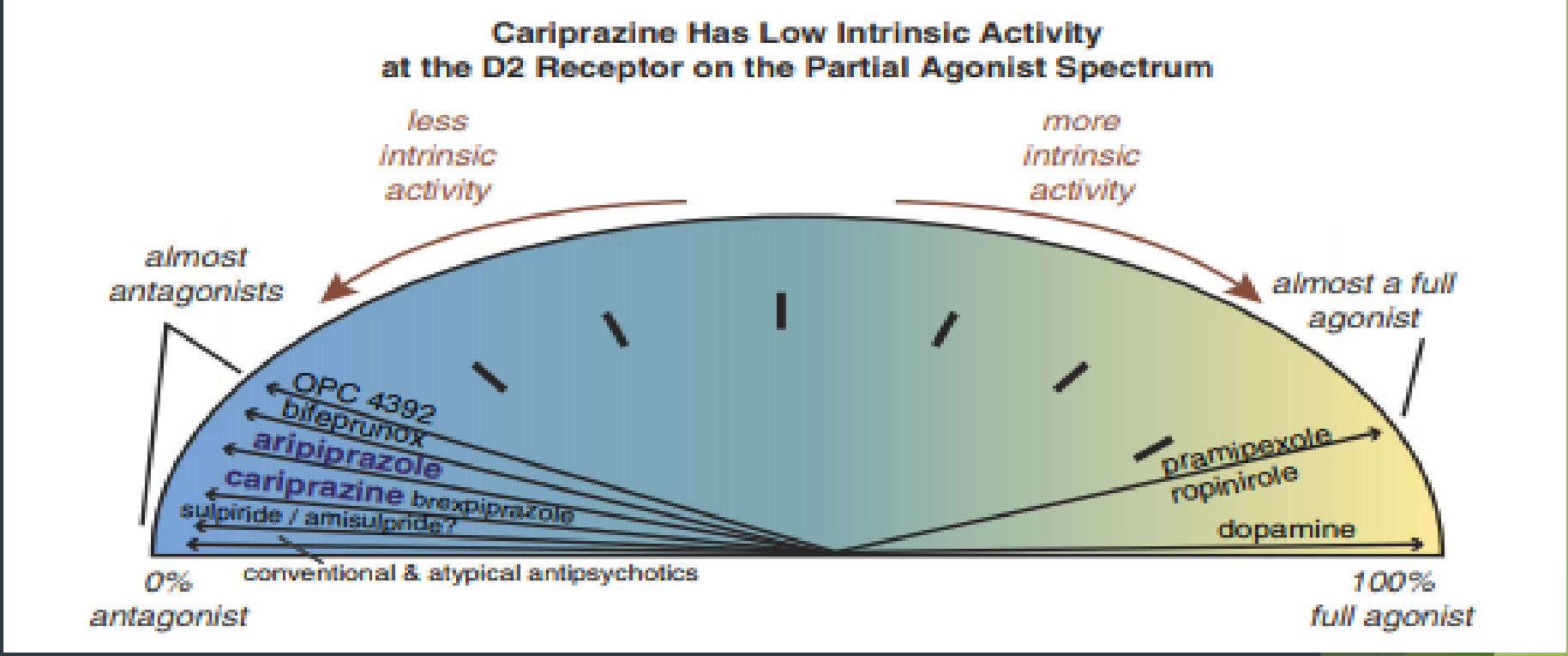
Glutamergic Agents (Total)	6		
Memantine	3	134	−0.95 [−2.04, 0.14]
Glycine	3	58	−0.32 [−0.84, 0.20]
Sarcosine	1	20	0.26 [−0.62, 1.14]
Glutamergic Agents (Positive)			
Memantine			−0.28 [−0.94, 0.38]
Glycine			−0.63 [−1.48, 0.21]
Sarcosine	1	20	0.50 [−0.40, 1.39]
Glutamergic Agents (Negative)	6		
Memantine	3	134	−0.56 [−0.93, −0.20]*
Glycine	3	58	−0.03 [−0.57, 0.51]
Sarcosine	1	20	0.10 [−0.77, 0.98]
Other agents			
Minocycline (Total)	1	50	−0.46 [−1.03, 0.10]
Minocycline (Positive)	1	50	−0.40 [−0.96, 0.16]
Minocycline (Negative)	1	50	−0.58 [−1.15, −0.01]*
Gingko (Total)	1	38	−2.35 [−3.20, −1.50]*
Gingko (Negative)	1	42	−1.10 [−1.75, −0.44]*

MOST EFFECTIVE AUGMENTATION FOR NEGATIVE SYMPTOMPS WAS MEMANTINE

Siskind DJ et al, Aust NZJ Psy (2018)


TREATMENT RESISTANCE
RESIDUAL SYMPTOMS
REDUCE FIRST APs' DOSAGES
Rationale for clozapine add-on to partial agonists
RELAPSE PREVENTION
SUICIDALITY
DOPAMINE SUPERSENSITIVITY PSYCHOSIS
MANAGING SIDE EFFECTS

The dopamine agonist spectrum goes from “silent” antagonism on the far left to “full” agonism on the right



- Aripiprazole has a bit less intrinsic activity, yet its clinical profile of activation, agitation, and akathisia in some patients suggests that it has too much intrinsic activity for them.
- Both cariprazine and brexiprazole “dialed down” the intrinsic activity another notch, to theoretically generate receptor binding properties at the D2 receptor that would make it less activating and possibly have a better overall tolerability profile.

Stahl, CNS Spectrums, 2016;21:123–127

Antipsychotics augmentation strategies for clozapine in TRS

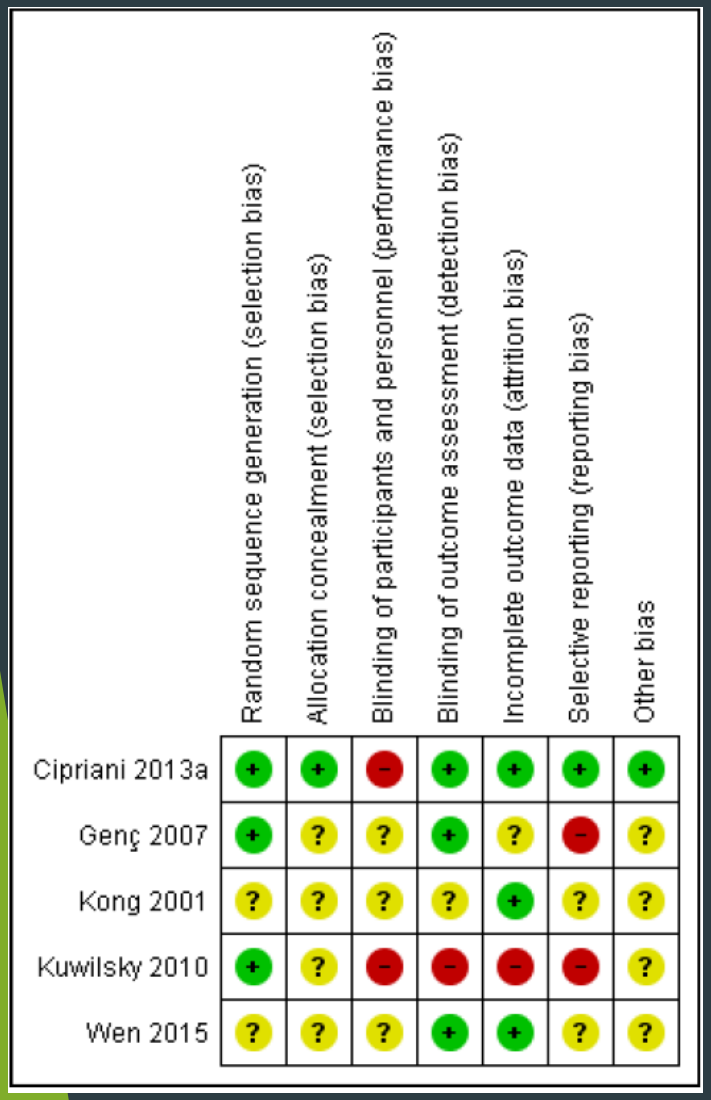
Agent	Studies	Participants	Std. mean difference (Random, 95% CI)
Antipsychotics (Total)	15		
Aripiprazole	7	486	−0.57 [−1.02, −0.13]*
Risperidone	3	144	−0.18 [−0.71, 0.36]
Sulpride/Amisulpride	2	85	−0.44 [−1.05, 0.16]
Sertindole	1	50	−0.08 [−0.64, 0.47]
Pimozide	1	53	0.27 [−0.27, 0.81]
Antipsychotics (Positive)	11		
Aripiprazole			−0.15 [−0.60, 0.30]
Risperidone			−0.03 [−0.50, 0.45]
Sulpride			−0.77 [−1.55, 0.01]
Sertindole			0.00 [−0.55, 0.55]
Pimozide			−0.09 [−0.63, 0.45]
Olanzapine			0.31 [−0.25, 0.87]
Antipsychotics (Negative)	11		
Aripiprazole	5	328	−0.33 [−0.55, −0.11]*
Risperidone	3	144	−0.20 [−0.53, 0.13]
Sertindole	1	50	0.00 [−0.55, 0.55]
Pimozide	1	53	0.48 [−0.06, 1.03]
Sulpride/Amisulpride	2	85	−0.32 [−1.06, 0.41]
Olanzapine	1	50	−1.14 [−1.74, −0.54]*

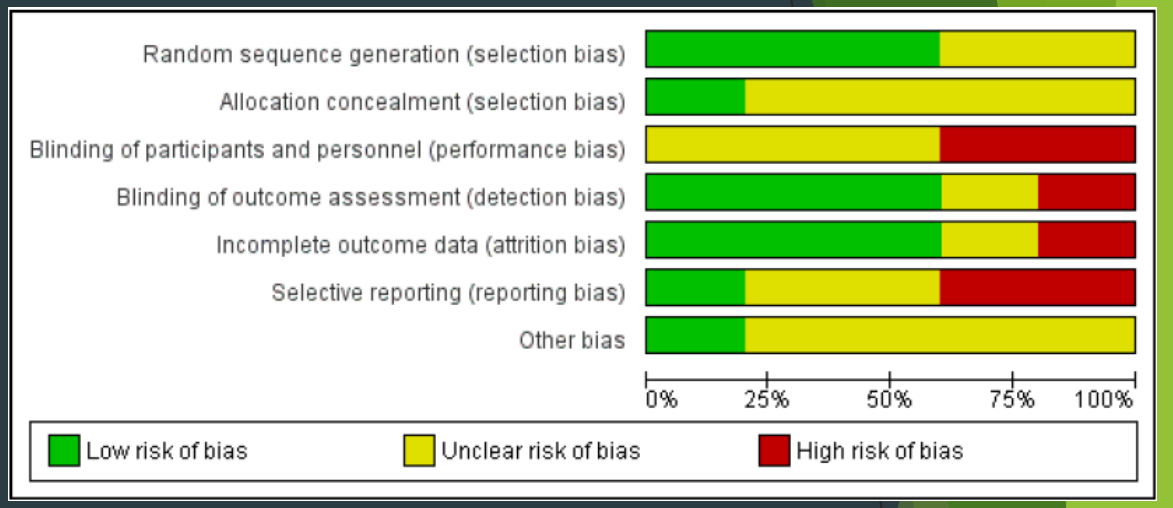
MOST EFFECTIVE AUGMENTATION WAS ARIPIPRAZOLE (5HT1 agonism)
On overall positive, and negative symptoms

The efficacy of Aripiprazole for pts with TRS is delayed and can be observed only after several months of augmentation

Siskind DJ et al, Aust NZJ Psy (2018)

Quality of studies

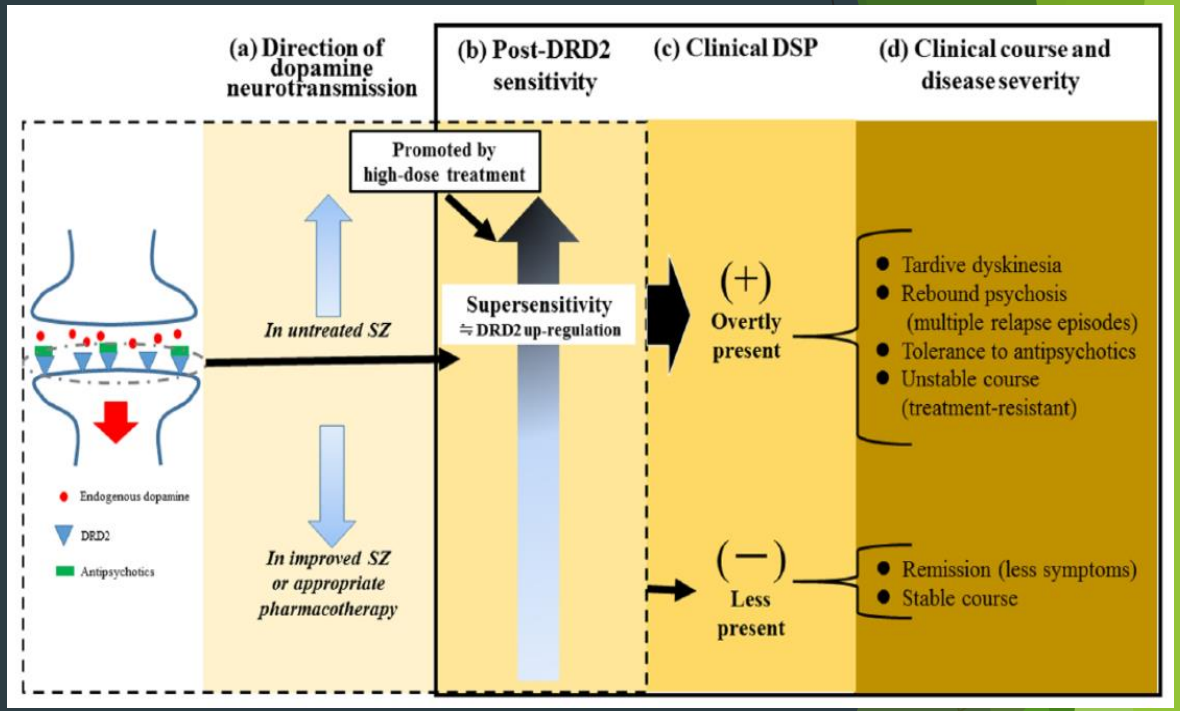




Risk of bias in allocation, in blinding, in incomplete outcome data, in selective reporting or in other potential sources was judged as often unclear

Dopamine supersensitivity psychosis

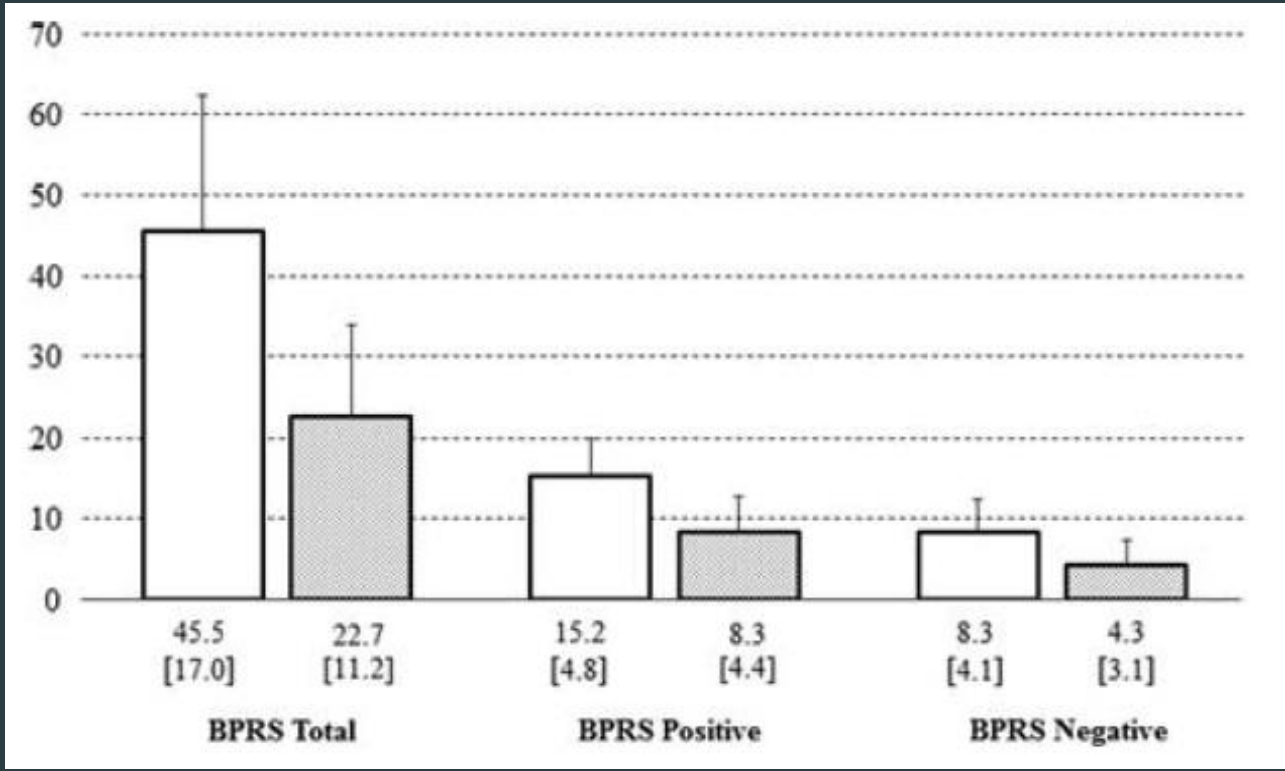
- Neuroleptic-induced D2 receptors upregulation (1970), requiring increasing doses of antipsychotics to control psychosis, with additional risk for tardive diskinesia
- Treatment resistant schizophrenia vs dopamine supersensitivity psychosis
- Increase risk for AP with short half-life, high potency and high dosage



Aripiprazole may prevent DSP, but it's not likely to treat it

Nakata Y et al, J Pychopharm (2018)

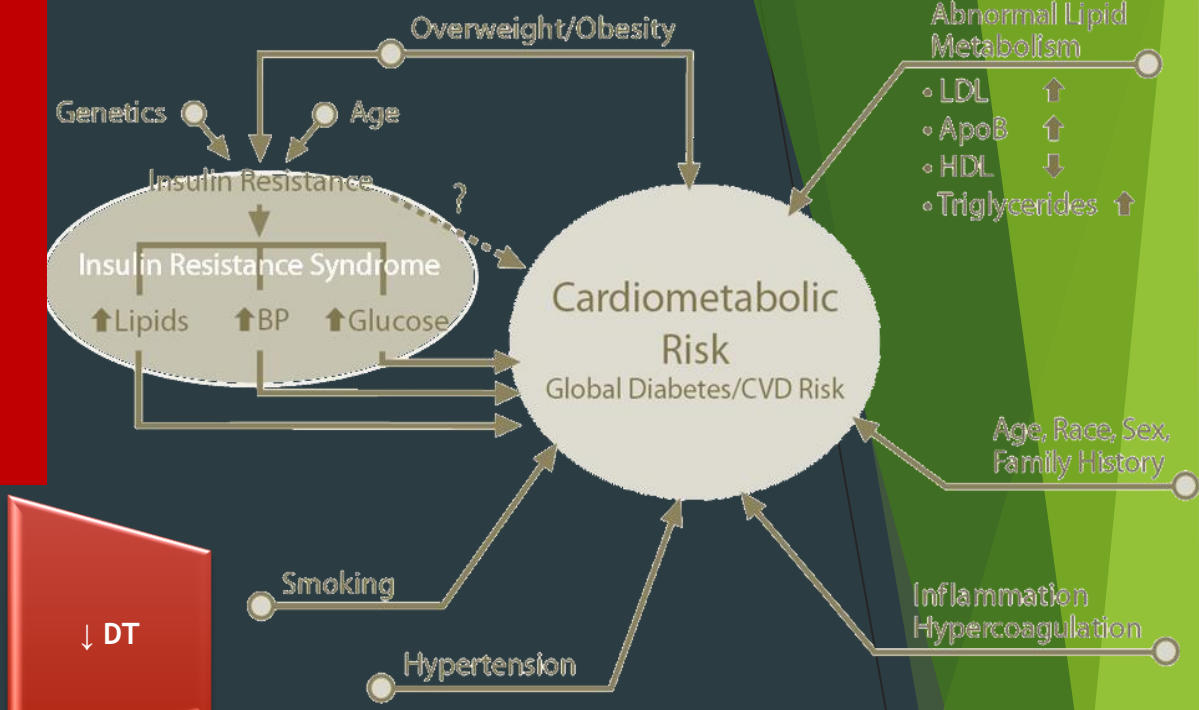
Clozapine efficacy in dopamine supersensitivity psychosis



Clozapine ameliorates dopamine supersensitivity states

Nakata Y et al, Int Clin Psychopharm (2017)

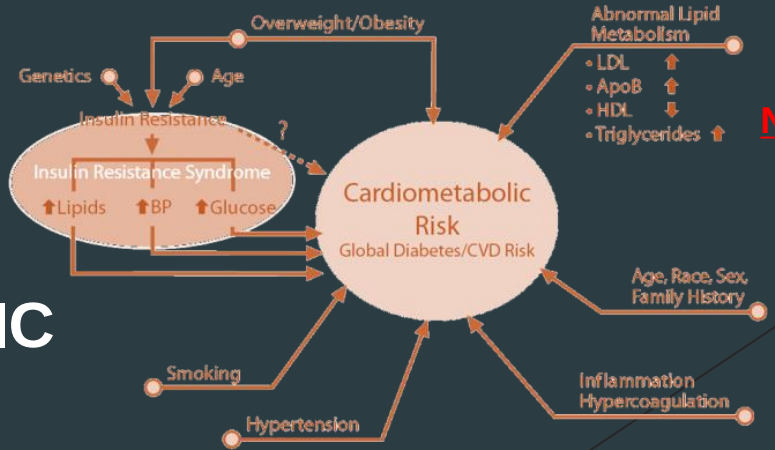
Antipsychotics Side Effects: WHAT HAS BEEN CHANGED?



Metabolic side effects → **Neurological side effects** → **↓ EPS** → **↓ DT**

2000 –2006 → **2006-2011** → **2006-2020**

ATYPICAL ANTIPSYCHOTIC ERA



Metabolic side effects

Neurological side effects

↑ DT

Selected side effects of commonly used antipsychotic medications [a]

Medications	EPS side effects/ TD	Prolactin elevation	Weight gain	Glucose abnormalities	Lipid abnormalities	QTs prolongation	Sedation	Hypotension	Anticholin. side effects
Thioridazine	+	++	+	+?	+?	+++	++	++	++
Perphenazine	++	++	+	+?	+?	0	+	+	0
Haloperidol	+++	+++	+	0	0	0	++	0	0
Clozapine[b]	0[c]	0	+++	+++	+++	0	+++	+++	+++
Risperidone	+	+++	++	++	++	+	+	+	0
Olanzapine	0[c]	0	+++	+++	+++	0	+	+	++
Quetiapine[d]	0[c]	0	++	++	++	0	++	++	0
Ziprasidone	0[c]	+	0	0	0	++	0	0	0
Aripiprazole[e]	0[c]	0	0	0	0	0	+	0	0

[a] 0= No risk or rarely causes side effects at therapeutic dose. + Mild or occasionally causes side effects at therapeutic dose. ++ Sometimes causes side effects at therapeutic dose. +++ Frequently causes side effects at therapeutic dose. ? Data too limited to rate with confidence. Adapted from Tandon (2007) with permission of Current Medicine, Inc.

[b] Also causes agranulocytosis, seizure, and myocarditis.

[c] Possible exception of akathisia.

[d] Also carries warning about potential development of cataracts.

[e] Also causes nausea and headache.

Practice Guidelines for the treatment of patients with schizophrenia, APA 2004

Safety, tolerability, and risks associated with first- and second-generation antipsychotics: a state of the art clinical review

Drug	K_i D2	K_i 5HT1A	K_i 5HT2A	K_i 5HT2C	K_i α1	K_i α2	K_i H1	K_i M2
CPZ	*3*	*2,115*	*4.06*	*32.5*	*2.6*	*750*	*3*	*244*
HAL	*2.6*	*1,800*	*61*	*4,700*	*17*	*600*	*260*	*>10,000*
LOX	*9.8*	*NA*	*2*	*NA*	*250*	*NA*	*14.9*	*NA*
MOL	*120*	*3,797*	*5,000*	*>10,000*	*2,500*	*625*	*>10,000*	*NA*
PER	*1.4*	*421*	*5*	*132*	*10*	*500*	*8*	*NA*
AMI	1.3	>10,000	2,000	>10,000	7,100	1,600	>10,000	NA
ARI	±0.7	±5.5	8.7	22	26	74	30	3,510
ASE	1.3	2.5	0.06	0.03	1.2	1.2	1	>10,000
BRE	±0.3	±0.12	0.47	NA	3.8	0.59	19	NA
CAR	±0.5	±2.6	18.8	134	155	NA	23.2	>10,000
CLO	210	160	2.59	4.8	6.8	158	3.1	204
ILO	6.3	168	5.6	14	4.7	4.7	437	3,311
LUR	1	±6.4	0.5	NA	NA	11	>10,000	>10,000
OLA	20	610	1.5	4.1	44	280	0.1	622
PALI	2.8	480	1.2	48	10	80	3.4	>10,000
RIS	3.8	190	0.1	32	2.7	8	5.2	>10,000
QUE	770	300	31	3,500	8.1	80	19	630
SER	2.7	2,200	0.14	6	3.9	190	440	NA
ZIP	4.8	±3.4	0.4	1.3	10	154	4.6	>3,000
Effects related to receptor blockade								
	EPS, hyperprolactinemia, sexual dysfunction, and cognitive dysfunction	Anxiolytic and antidepressant effects	Lower incidence of akathisia and parkinsonism	Weight gain and metabolic effects	Hypotension, priapism, retrograde ejaculation, and low libido	Antidepressant	Appetite, sedation, cognitive dysfunction, and weight gain	Cognitive dysfunction, urinary retention, glaucoma, constipation, and dry mouth

Solmi et al., Therapeutics Clin Risk Management 2017; 13: 757–777

Clozapine and side effects

Common	Uncommon	Rare
Sedation	Agranulocytosis (LT)	Myocarditis/pericarditis (LT)
Hypertension	Diabetes mellitus/ hyperglycemia/DKA (LT)	Cardiomyopathy (LT)
Weight gain	Metabolic syndrome	Heat stroke (LT)
Seizures (LT)	Delirium	Hepatic failure (LT)
Hypersalivation or sialorrhea	Liver enzyme abnormalities	Colitis (LT)
Benign fever	Interstitial nephritis	Intestinal obstruction/ paralytic ileus (LT)
Hypotension	Stuttering	Pancreatitis (LT)
Nausea	Thrombocytopenia	Pneumonia (LT)
Nocturnal enuresis	Dysphonia	Respiratory failure (LT)
Gastroesophageal reflux	Neuroleptic malignant syndrome (LT)	Vasculitis
Constipation		Skin rash
Tachycardia		Ocular pigmentation
Dizziness		Priapism
Blurred vision		Parotid gland swelling
Dysarthria		Rhabdomyolysis
Blood dyscrasias such as leukopenia/ decreased WBC/neutropenia/ eosinophilia/leukocytosis		QT prolongation (LT)
		Sudden death (LT)

De Berardis et al, Ther Adv in Drug Safety (2018)

Clozapine and Agranulocytosis/granulocytopenia

- Risk of respectively 0.8% and 3%, dose independent
- 50-75% occurring in the first 18 weeks and up to 90% within the first year of treatment with clozapine (after the first year, same risk of chloropromazine 0,13%)
- Cumulative risk for neutropenia decrease with age
- Cumulative risk for agranulocytosis increase with age (peak 40-50yy)
- Increase predisposition if alterations in CYP450 1A2/3A4, P-gp or HLA polymorphisms?

Direct toxic process from nitrenium ion (ROS derived from result of dehydrogenation of the piperazine-ring of clozapine or its metabolites)

Immuno-mediated response against haptenized neutrophils

Wicinski et al, Curr Opin Hematol (2018)

Clozapine and myocarditis

- Risk of 0,1-0,19% for myocardytis/cardiomyophaty during clozapine treatment, resulting in 10-46% (21%) mortality
- Not dose-dependent
- Common symptoms are dyspnea, palpitations, tachycardia, fever, fatigue, and chest pain (even non-specific simptoms such as malaise, diarrhea, headache and neck pain)
- Cardiologic signs may be sinus tachycardia and T-wave inversion
- May be asymptomathic
- Higher risk in the first 3 weeks
- 100% sensitivity for myocarditis if elevation in both troponins and CRP
- Eosinophilia often occurs after myocarditis development
- Probably safer slow titration (up to 25mg/die)
- Re-challenge with clozapine may be done only under close monitoring

Knoph KN et al, Schiz Res (2018)
Bellissima BL et al, I J of Card (2018)

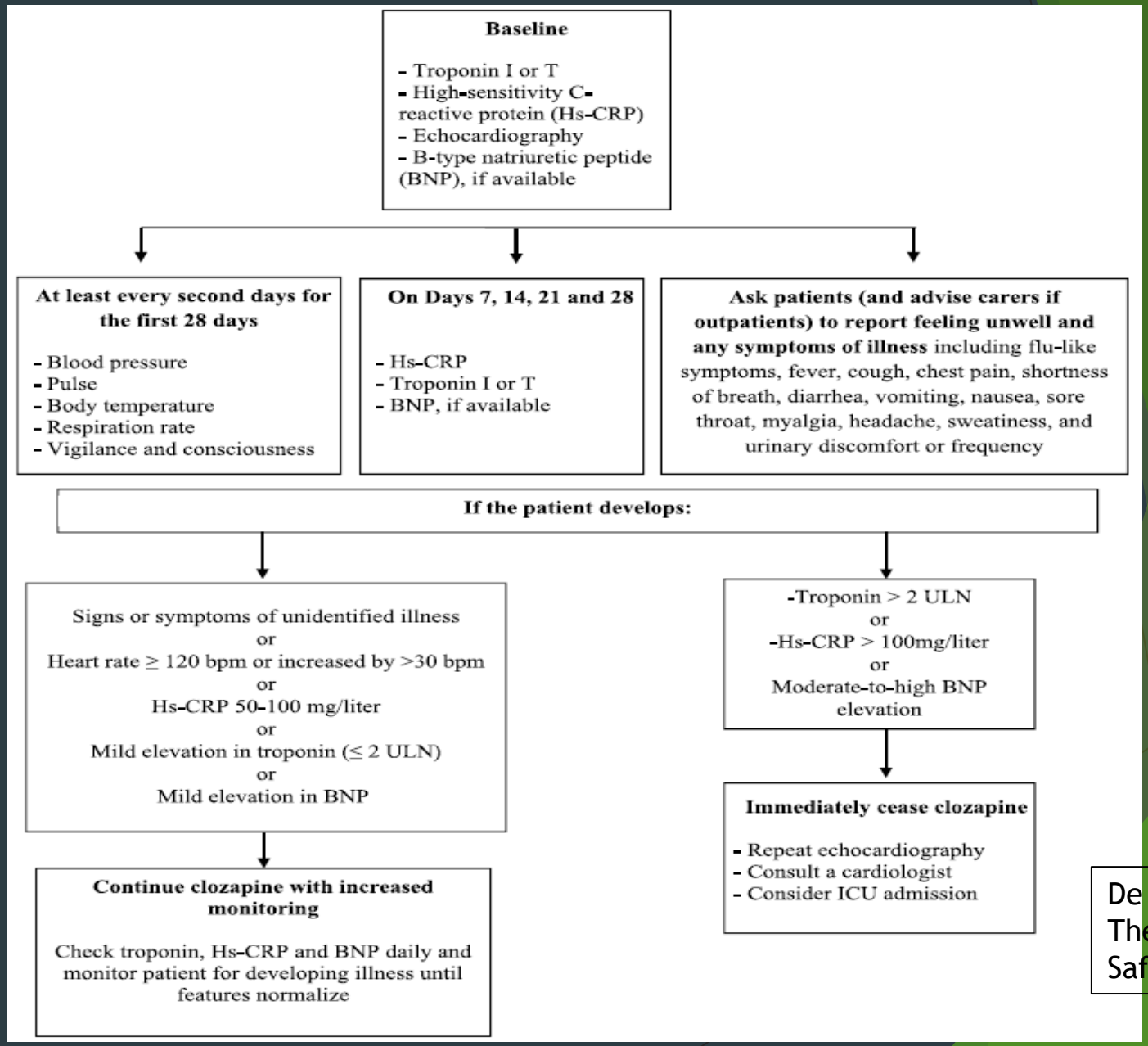
Pros and cons of clozapine add-on

- Clozapine is not likely to produce EPS, Hyper PRL or tardive diskinesia (no catalepsy in clinical studies)
- Superior efficacy compared to other APs
- Indication for suicidality

- Need to monitor for sever neutropenia (0,8%) or neutropenia (3%)
- Check for myocarditis (1:500-10000) mostly in the first 2 months (90%)
- Combine with antiseizures medications if needed (10%, dose related)
- Risk for gastrointestinal hypomotility, weight gain and diabetes mellitus

Nucifora FC et al, Neurother (2017)

Clozapine monitoring

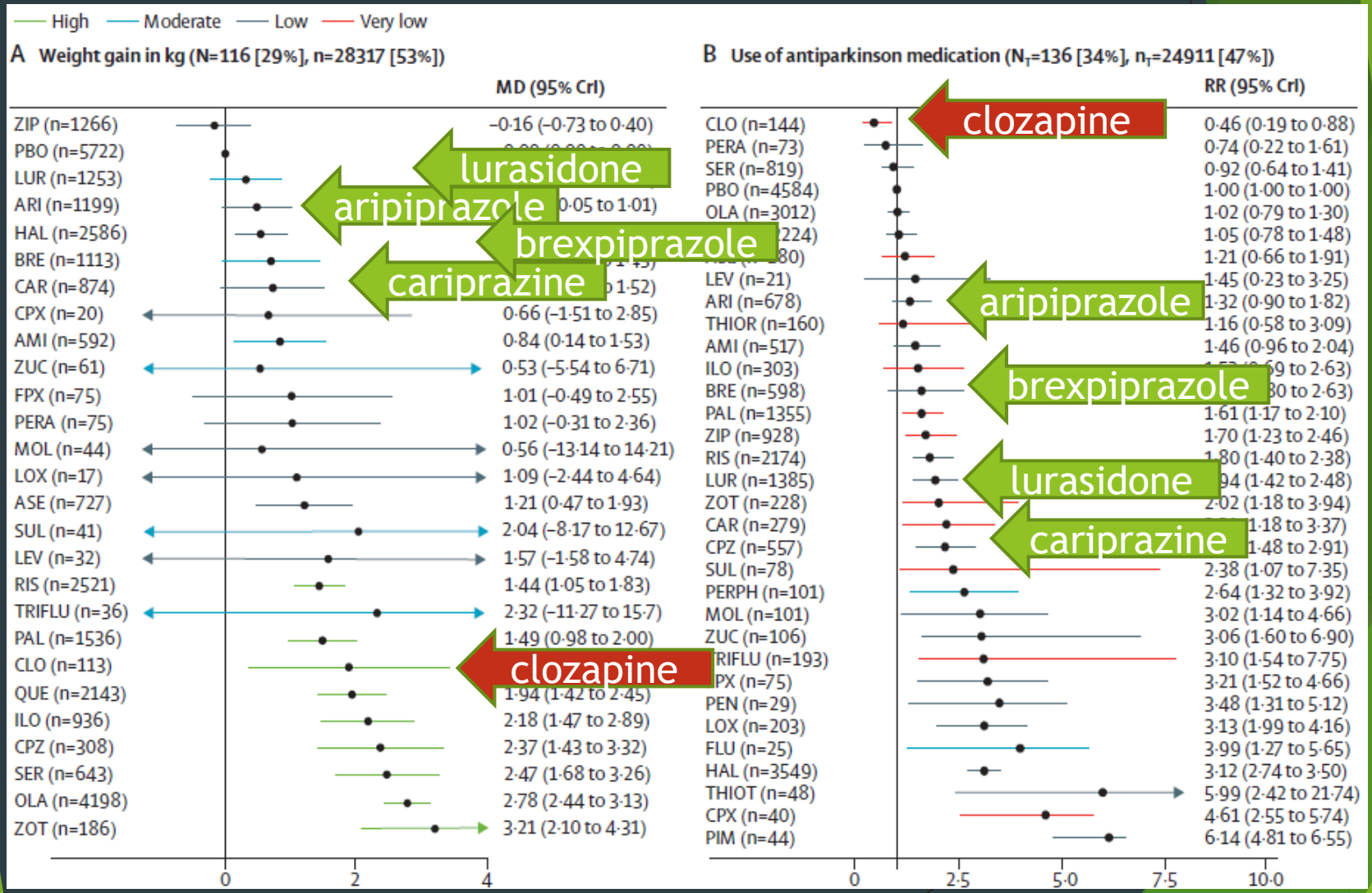


De Berardis et al, Ther Adv in Drug Safety (2018)

Add-on
Clozapine to
partial agonists

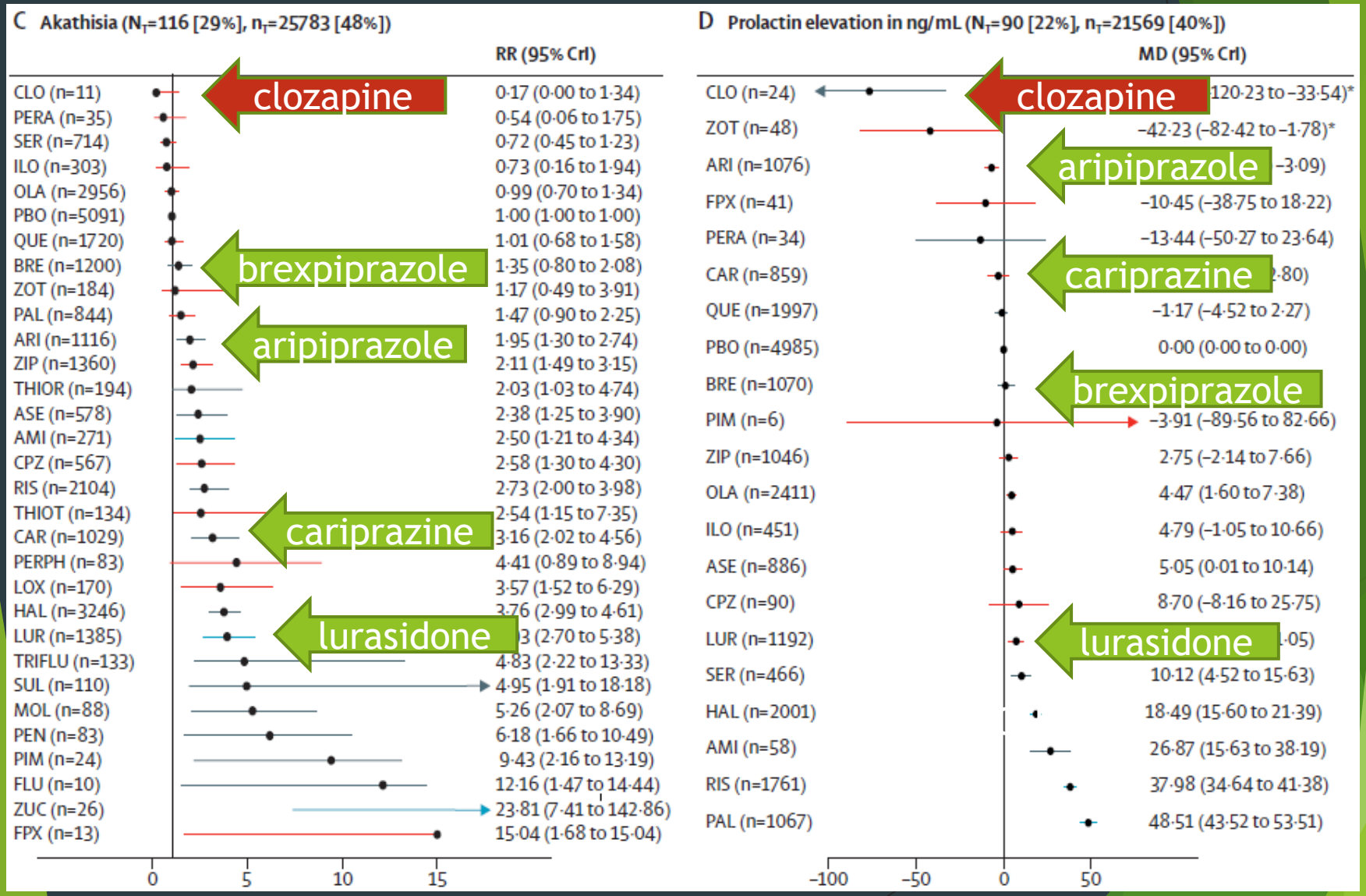
MANAGING SIDE EFFECTS

Safety and tollerability among APs
Weight gain and extrapyramidal symptoms



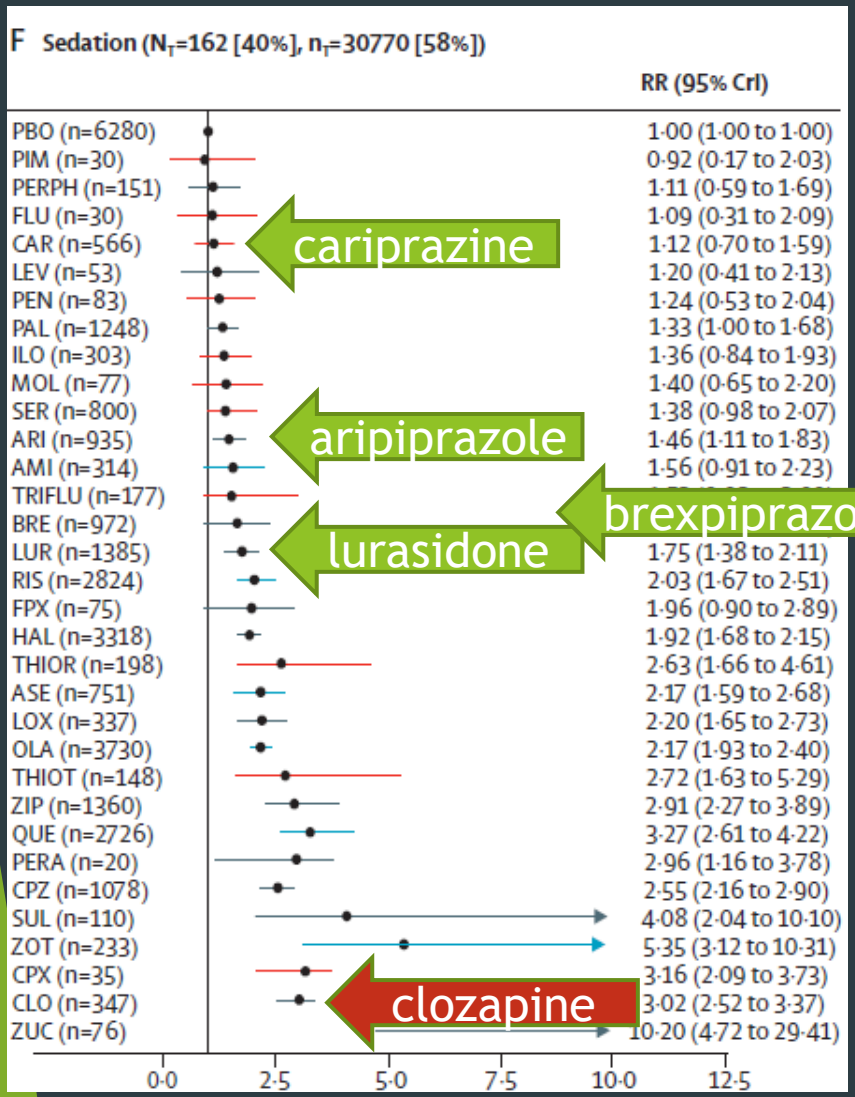
Huhn et al. ***Lancet*** 2019

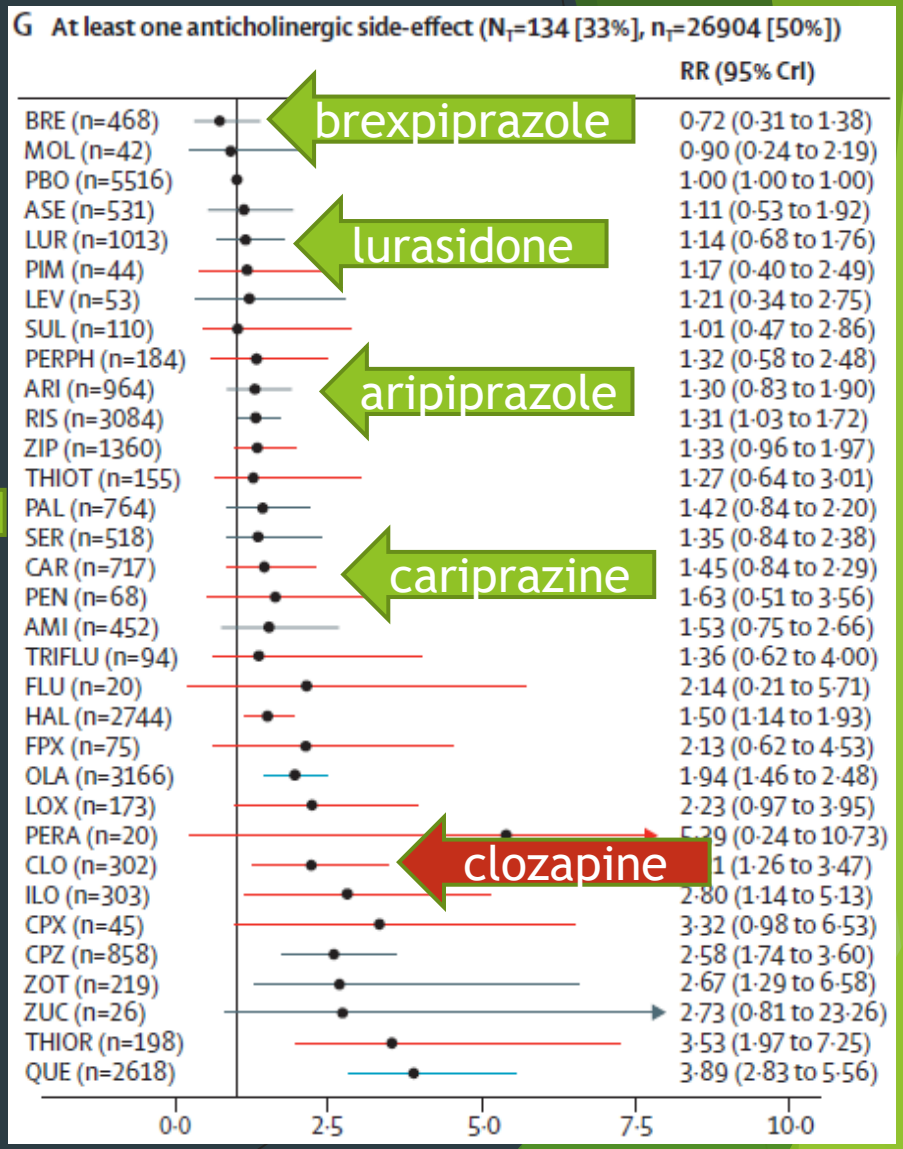
Safety and tollerability among APs
Akathisia and hyperprolactinemia



Huhn et al. ***Lancet*** 2019

Safety and tollerability among APs
Sedation and anticholinergic effect





Huhn et al. ***Lancet*** 2019

Schizophr Res. 2011 Apr;127(1-3):93-9. doi: 10.1016/j.schres.2010.12.011. Epub 2011 Jan 23.

Effect of aripiprazole augmentation of clozapine in schizophrenia: a double-blind, placebo-controlled study.

Muscatello MR[1], Bruno A, Pandolfo G, Micò U, Scimeca G, Di Nardo F, Santoro V, Spina E, Zoccali RA.

Clin Drug Investig. 2006;26(3):117-24.

Aripiprazole augmentation of clozapine in treatment-resistant schizophrenia: a clinical observation.

Ziegenbein M[1], Wittmann G, Kropp S.

J Child Adolesc Psychopharmacol. 2015 Nov;25(9):727-8. doi: 10.1089/cap.2015.0101. Epub 2015 Sep 24.

Effective Use of Aripiprazole Augmentation in a Clozapine-Treated Adolescent with Autism Spectrum Disorder.

Gunes H[1], Tanidir C[1], Erdogan A[1].

Indian J Pharmacol. 2015 Sep-Oct;47(5):574-5. doi: 10.4103/0253-7613.165176.

Aripiprazole as a treatment option for clozapine-induced enuresis.

Palaniappan P[1].

Contents lists available at ScienceDirect

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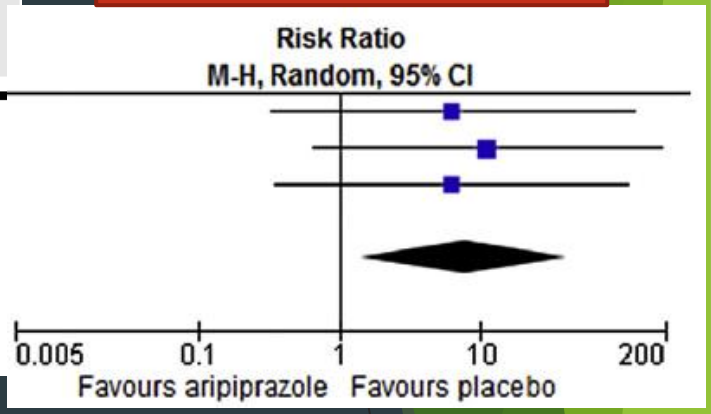
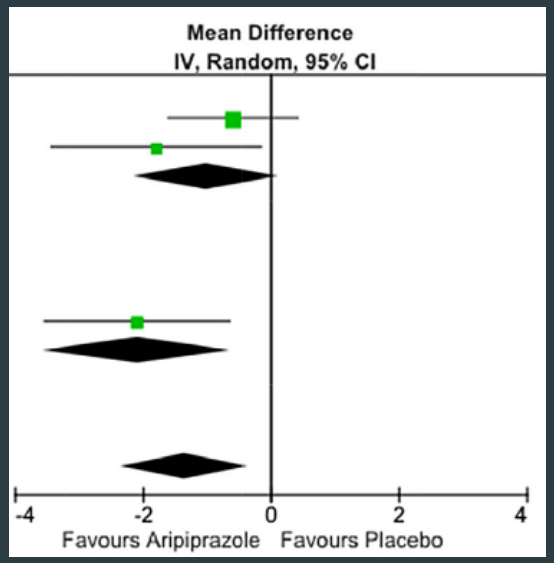
Efficacy and safety of aripiprazole augmentation of clozapine in schizophrenia: A systematic review and meta-analysis of randomized-controlled trials

Manit Srisurapanont*, Sirijit Suttajit, Narong Maneeton, Benchalak Maneeton

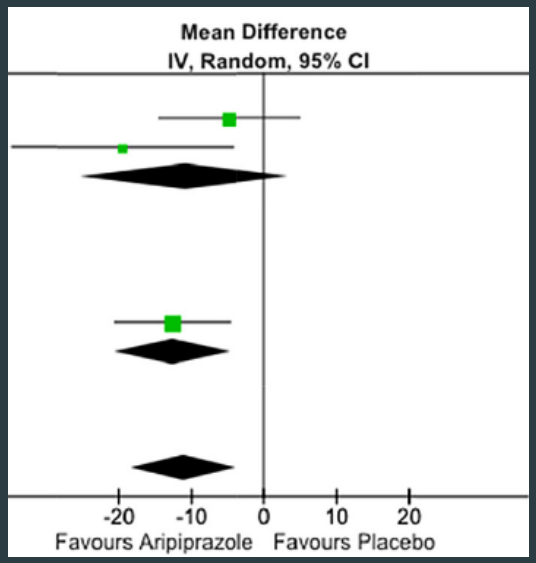
AGITATION/AKATHISIA



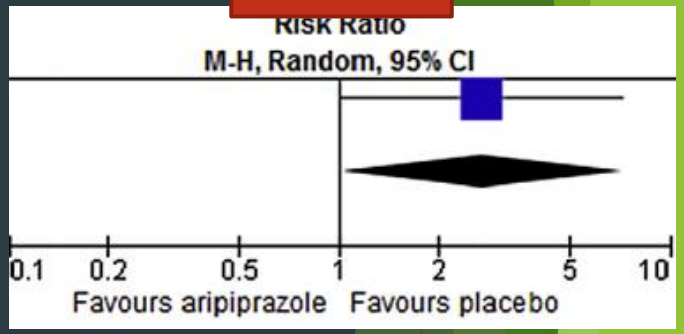
BODY WEIGHT



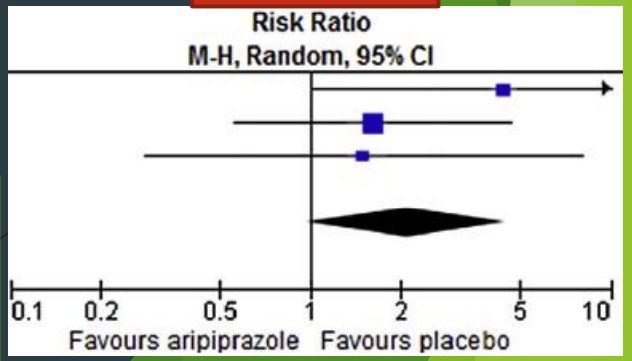
LDL



ANXIETY



INSOMNIA



Reduction in psychotic symptoms,body weight and LDL after add-on, but increasing in agitation, anxiety and insomnia

Take-home message

Further high quality studies are needed to assess efficacy as well as safety and tollerability of clozapine add-on to partial agonistis, but to date:

- **Add-on to D2 partial agonists may reduce positive symptoms**
- **Add-on to 5HT1 agonists may improve negative symptoms**
- **Add-on to NMDA antagonists or NMDA partial agonists seems to show no efficacy**
- **Safety and tollerability** seems to be the same as clozapine used in monotherapy, but because of lower dosages and to combination, some D2 partial agonists' **side effects may be decreased** (EPS, akathisia) **as well as some clozapine's collaterality** (cardiometabolic, weight gain, obsessions)