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Mental Health
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Antipsychotics

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What I'm going to say

- How do APS work?
- Adverse Effects
- How well do they work?
  - Efficacy
  - Effectiveness
- Best Use
  - Choice
  - Dosing
  - Adherence
  - Discontinuation

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DOPAMINE, PSYCHOSIS AND ANTIPSYCHOTICS

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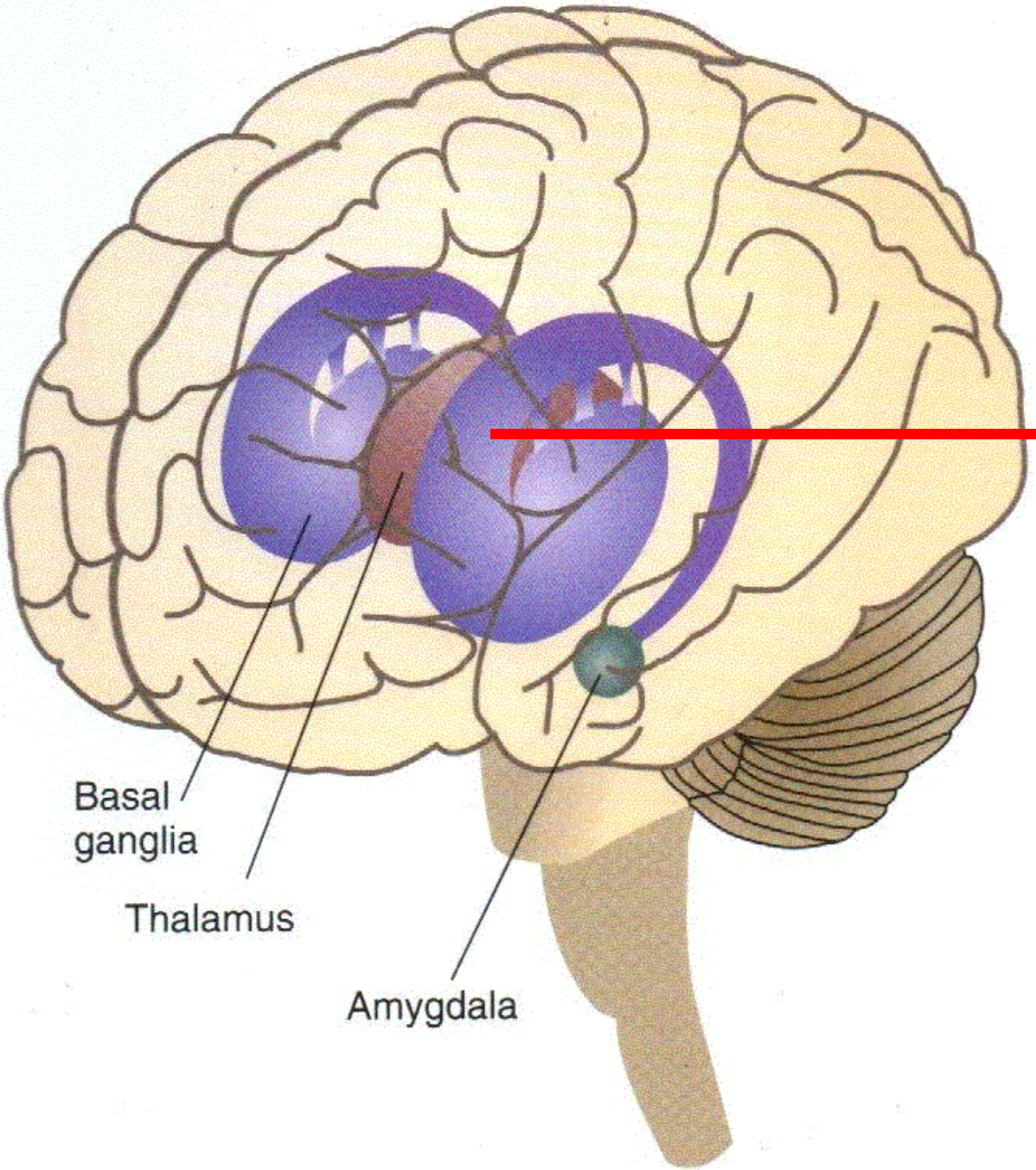
The Location of the Basal Ganglia in the Human Brain



Associative striatum

From: **Increased Synaptic Dopamine Function in Associative Regions of the Striatum in Schizophrenia**

Arch Gen Psychiatry. 2010;67(3):231-239. doi:10.1001/archgenpsychiatry.2010.10

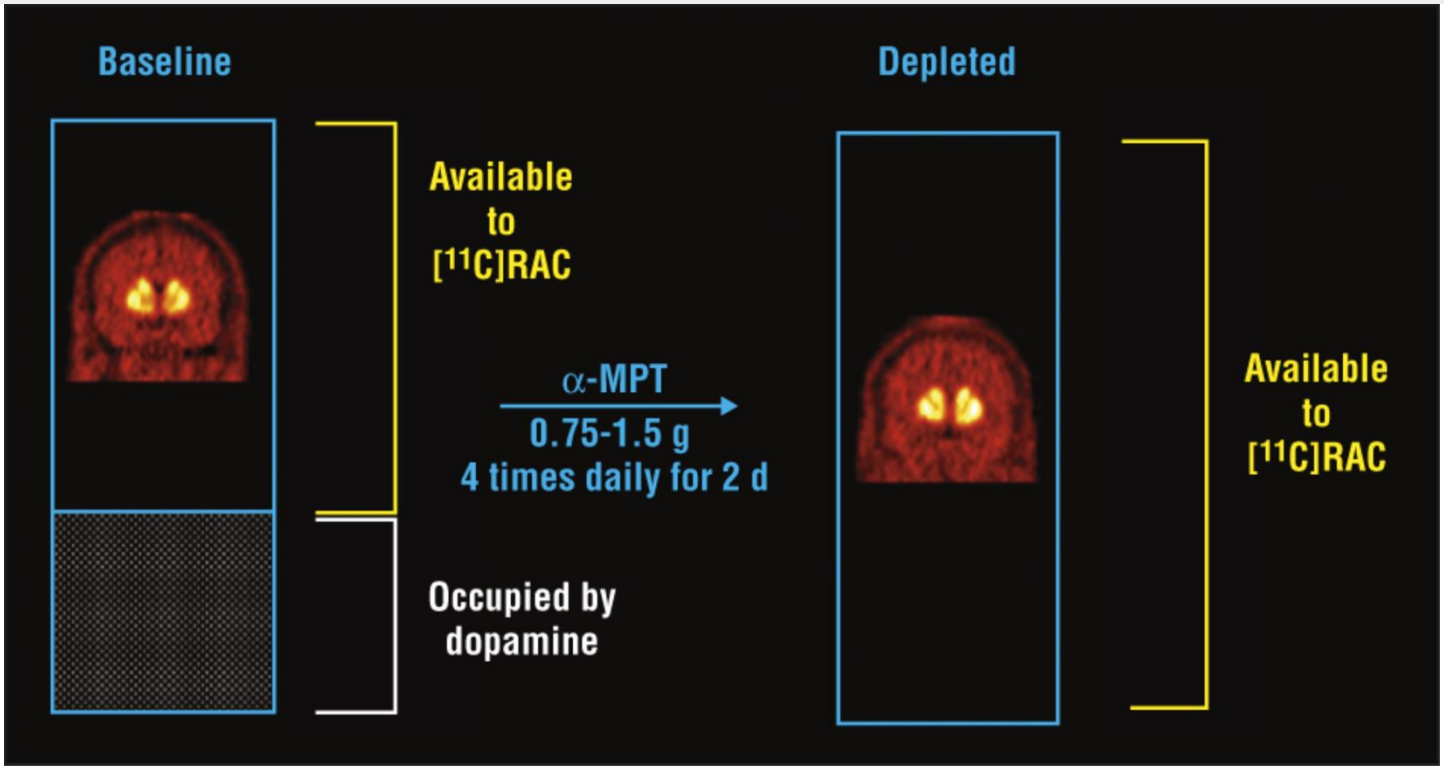
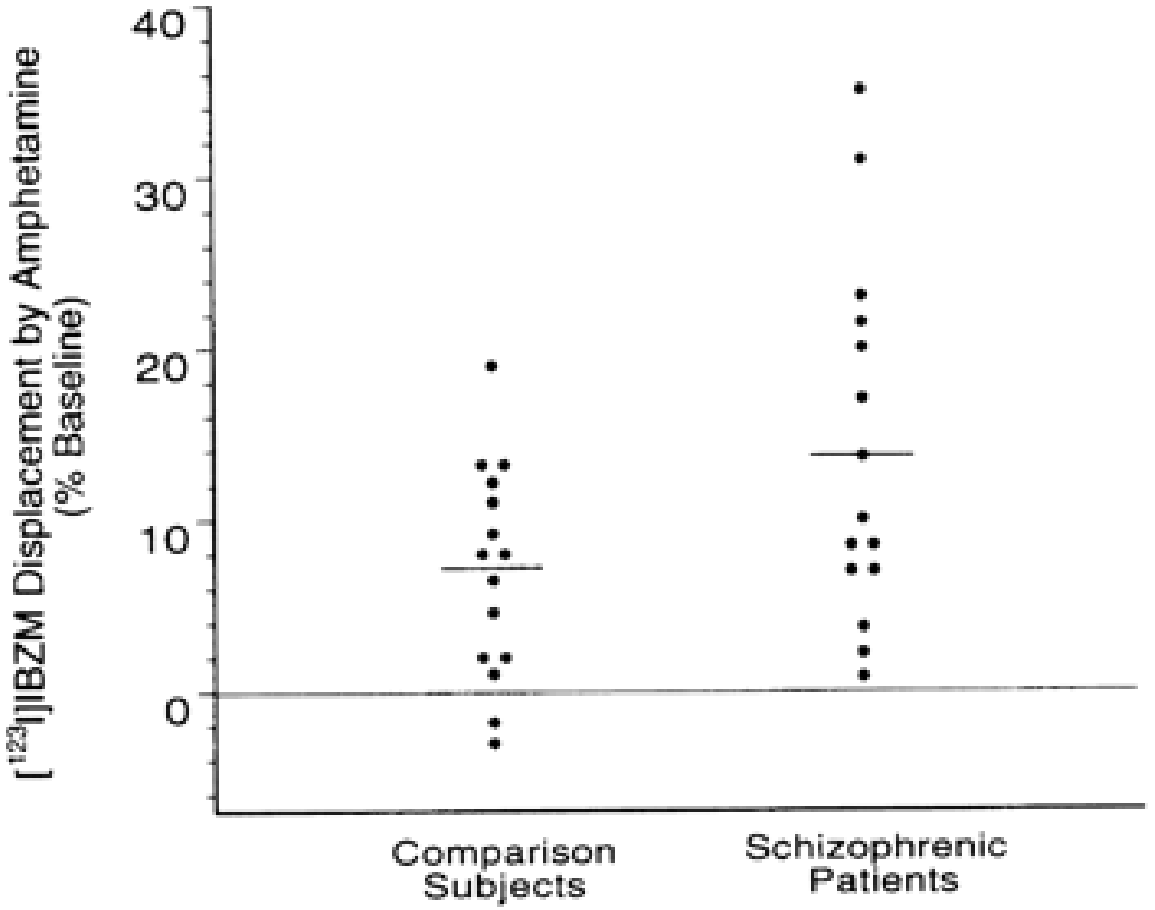


Figure Legend:

Schematic representation of the experiment. The blue rectangles represent the total population of D_2 receptors. At baseline, an unknown proportion of these receptors is occupied by dopamine (shaded area), and only a fraction of receptors are unoccupied and available to binding by carbon 11–labeled raclopride ([^{11}C]RAC). After depletion of endogenous dopamine induced by α-methylparatyrosine (α-MPT), all receptors are available to [^{11}C]RAC binding. Thus, comparing the [^{11}C]RAC binding potential at baseline and after dopamine depletion allows derivation of the proportion of D_2 receptors that were masked by dopamine at baseline.

FIGURE 3. Amphetamine-Induced Reduction in [^{123}I]IBZM Binding Potential in Healthy Subjects (N=15) and Schizophrenic Patients (N=15)[a]



[a]The amphetamine effect was significantly larger in schizophrenic patients (mean reduction of 13.8%, SD=10%, relative to baseline) than in healthy subjects (mean=7.1%, SD=6.2%) ($F=4.64$, $df=1, 28$, $p<0.05$). The horizontal line is the group average.

Abi-Dargham A. et al
Am J Psychiatry.1998;55:761– 767

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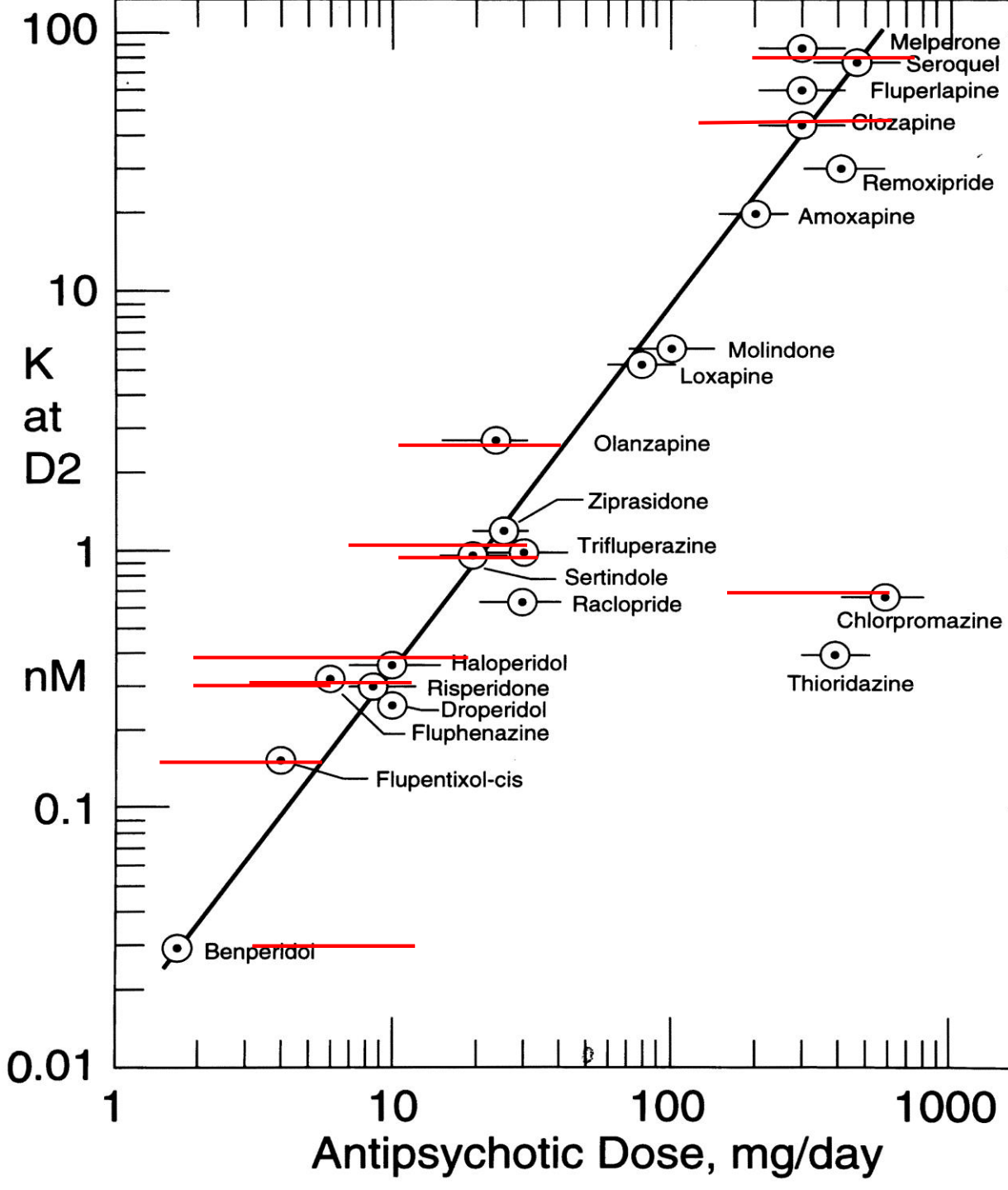
Seeman P.
Molecular Psychiatry
1998; 3:2; 123-34



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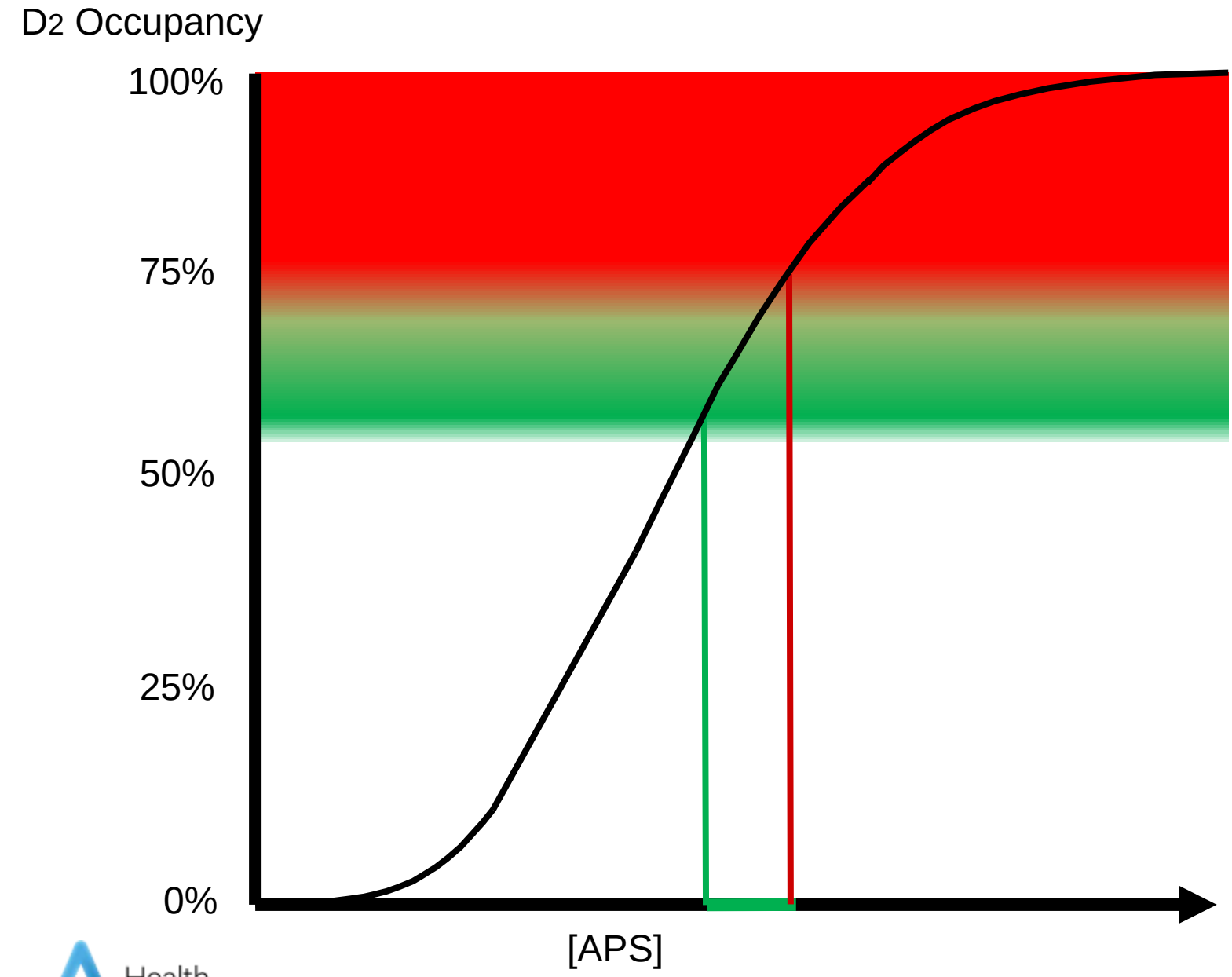

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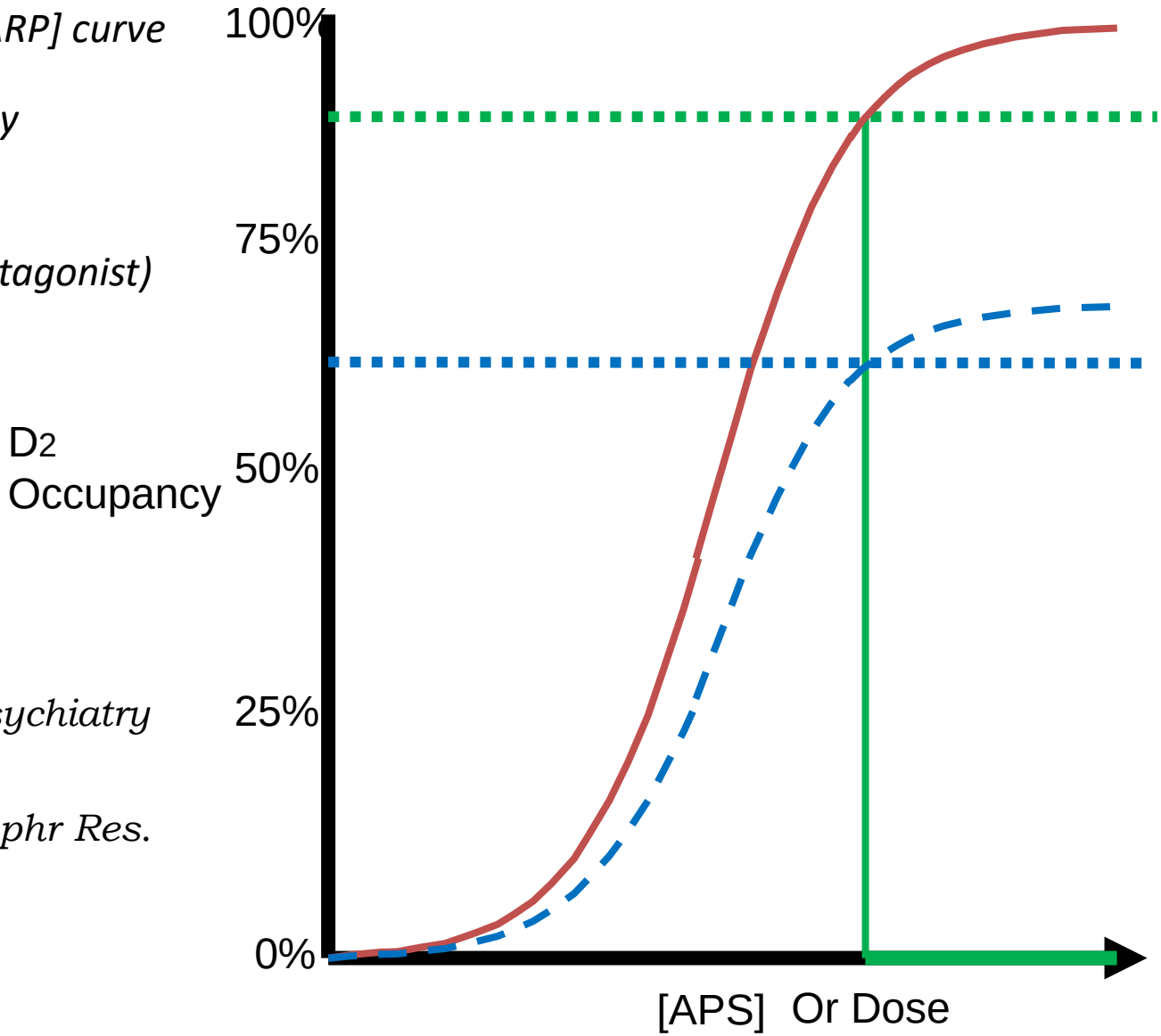
(after Uchida H et al. J Clin Psychopharmacol 2011;31: 497-502)

D_2 Receptor occupancy and Aripiprazole levels

Actual occupancy/[ARP] curve

Threshold for efficacy

Virtual effect (compared to full antagonist)



Sparshatt A et al. *J Clin Psychiatry* 2010;71(11):1447-56

Millikaarjun S et al. *Schizophr Res.* 2013;150:281-8

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SIDE EFFECTS

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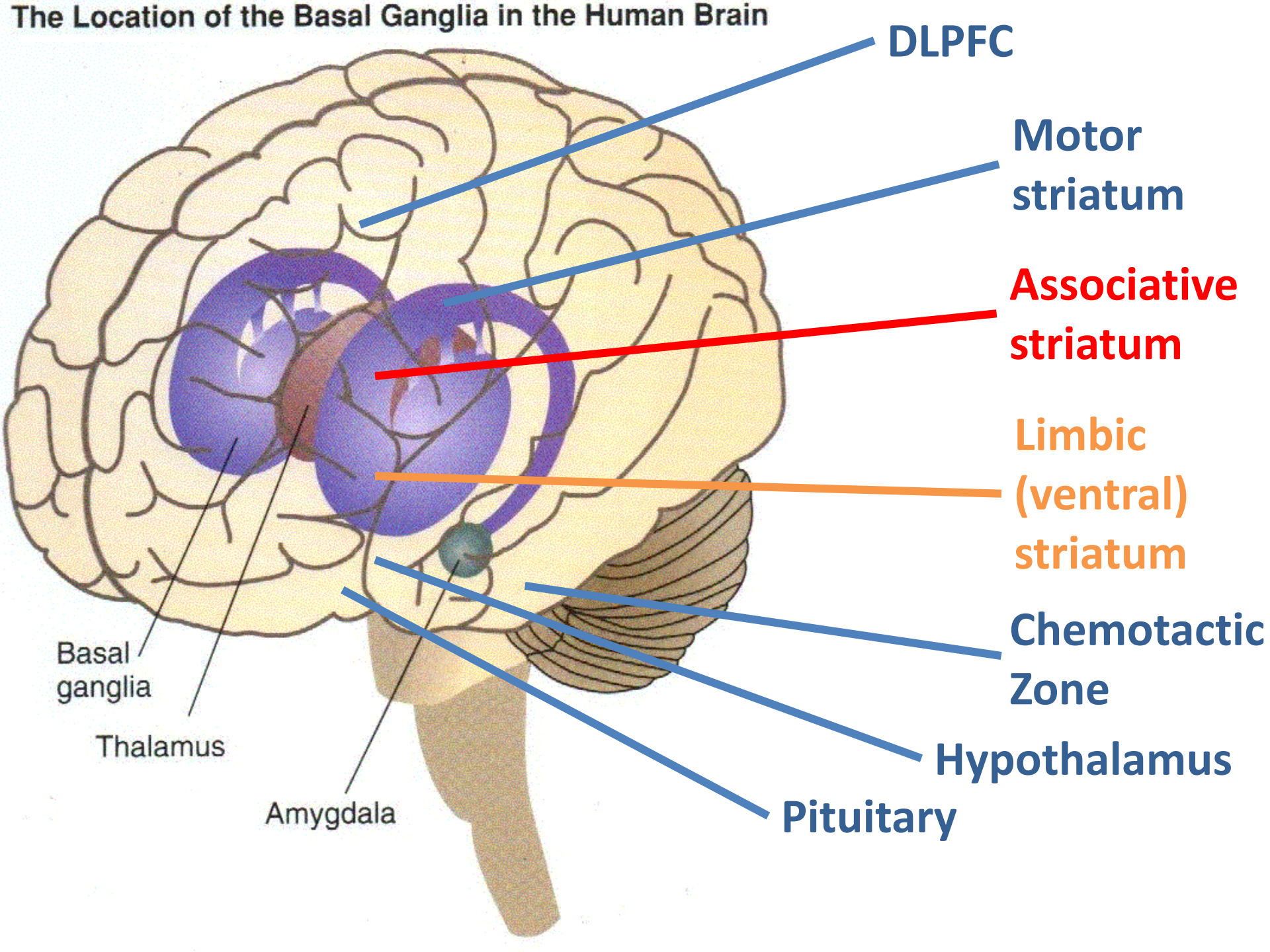
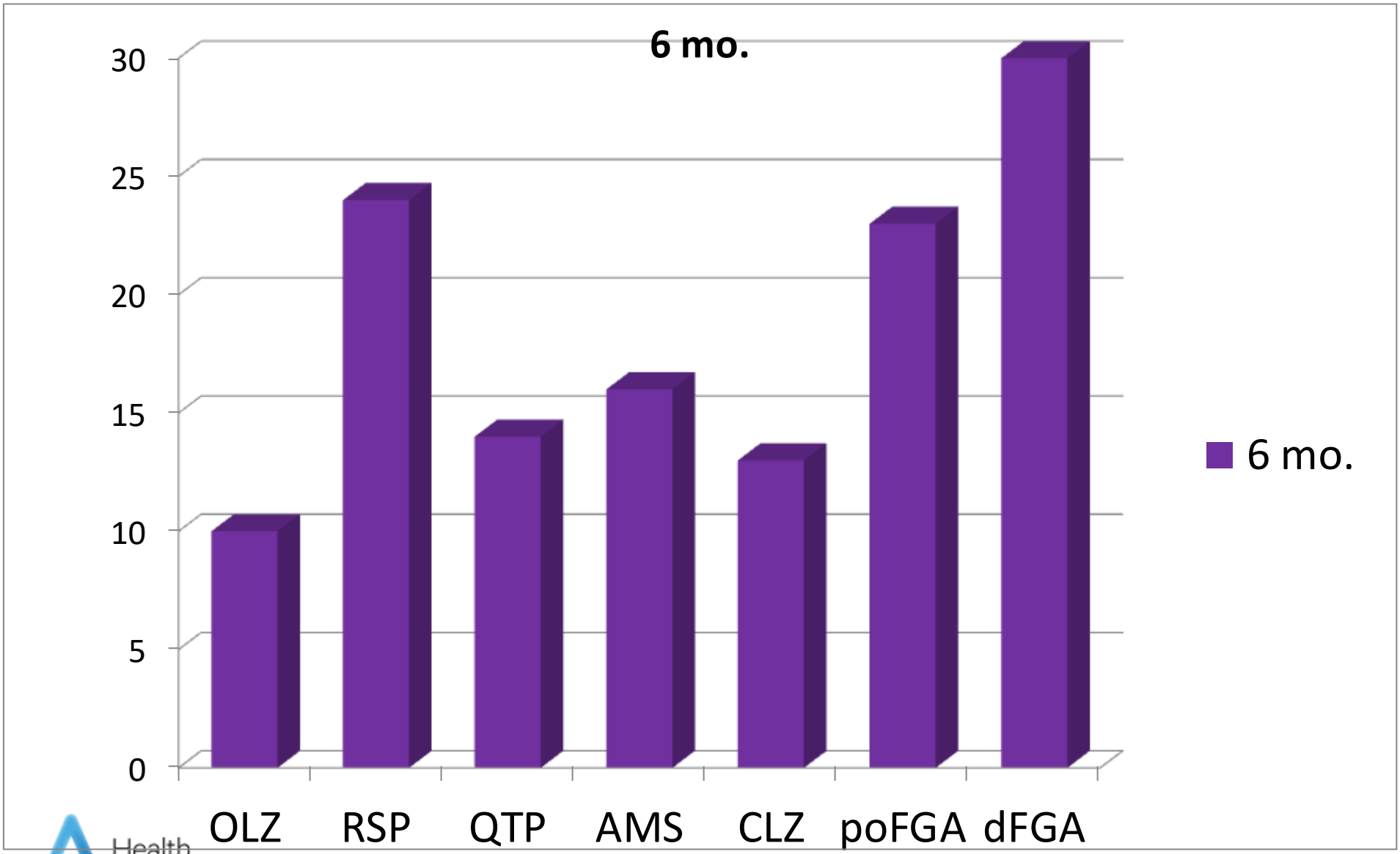

The Location of the Basal Ganglia in the Human Brain
DLPFC
Motor striatum
Associative striatum
Limbic (ventral) striatum
Chemotactic Zone
Hypothalamus
Pituitary
Basal ganglia
Thalamus
Amygdala

% movement side effects



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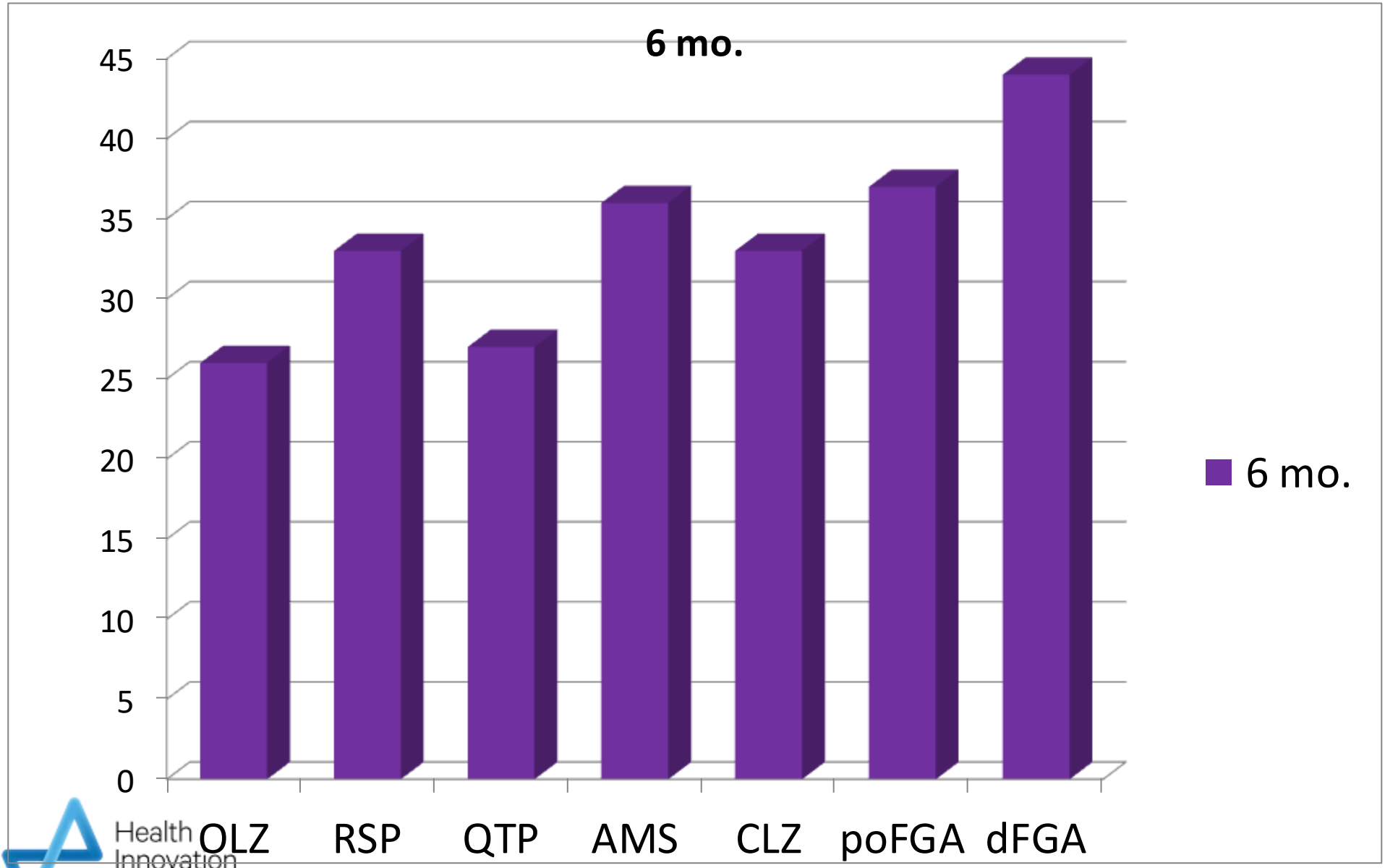
Lambert M et al. *Acta Psychiatr Scand* 2005: 111: 232–43

% Sexual Dysfunction



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Lambert M et al. *Acta Psychiatr Scand* 2005: 111: 232–43

Peripheral DA SE

- Constipation
  - Also ACh
- Arrhythmia?
  - Also ACh
- DM?
  - Also $5HT_2$

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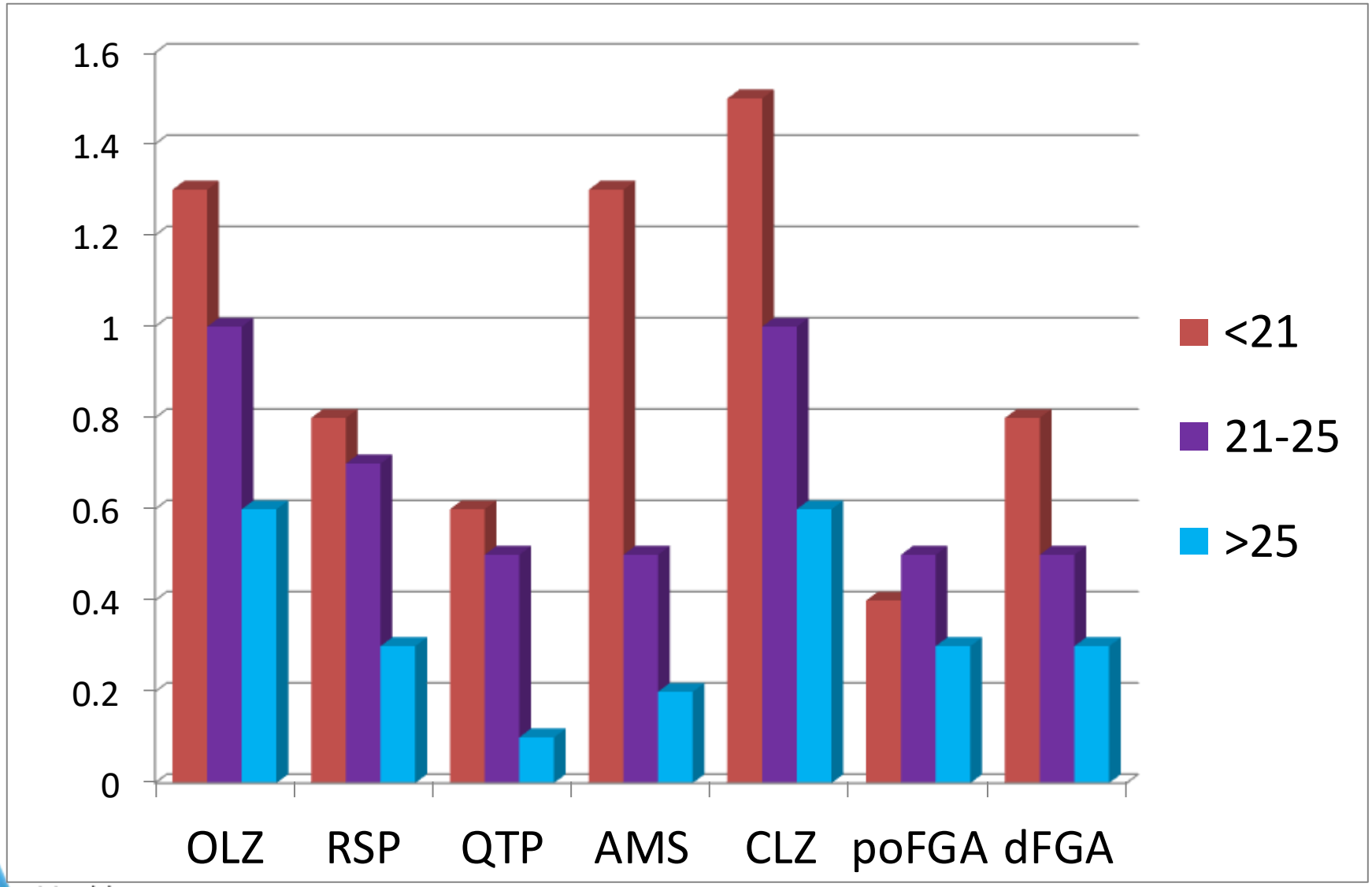
Non-DA SE

- ACh
  - Cardiac (tachycardia, arrhythmias)
  - GI (mouth, stomach, constipation)
  - urinary (retention)
  - eyes (dry, changed accommodation, dilated pupils)
  - central (reaction time, sedation, euphoria)
- α1
  - Reduced arousal, sedation; low BP (postural), cardiac
- 5HT1c, 5HT2
  - Sedation, appetite, mood, DM?
- H1
  - Sedation, appetite

Change in BMI



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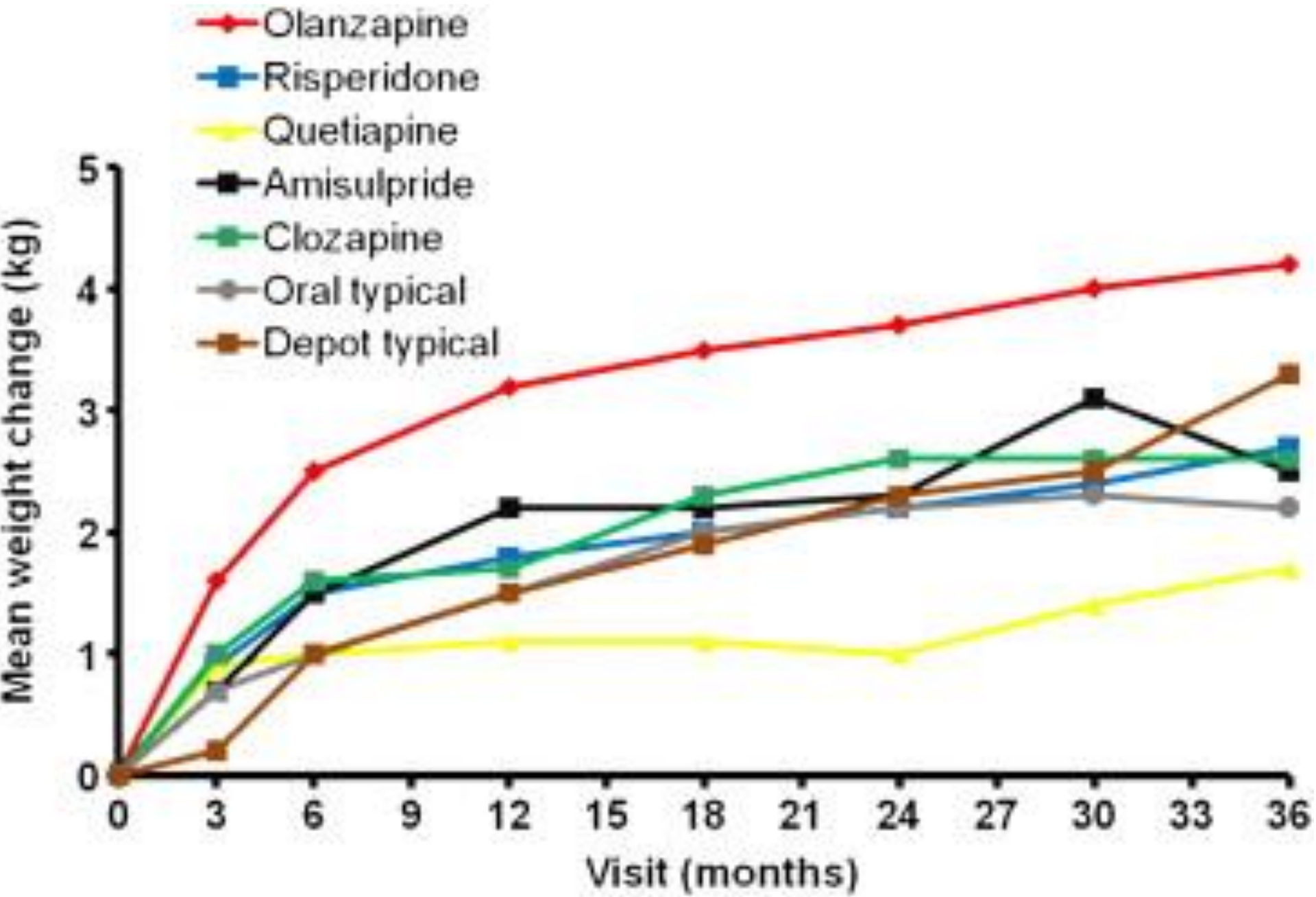
Lambert M et al. *Acta Psychiatr Scand* 2005: 111: 232–43



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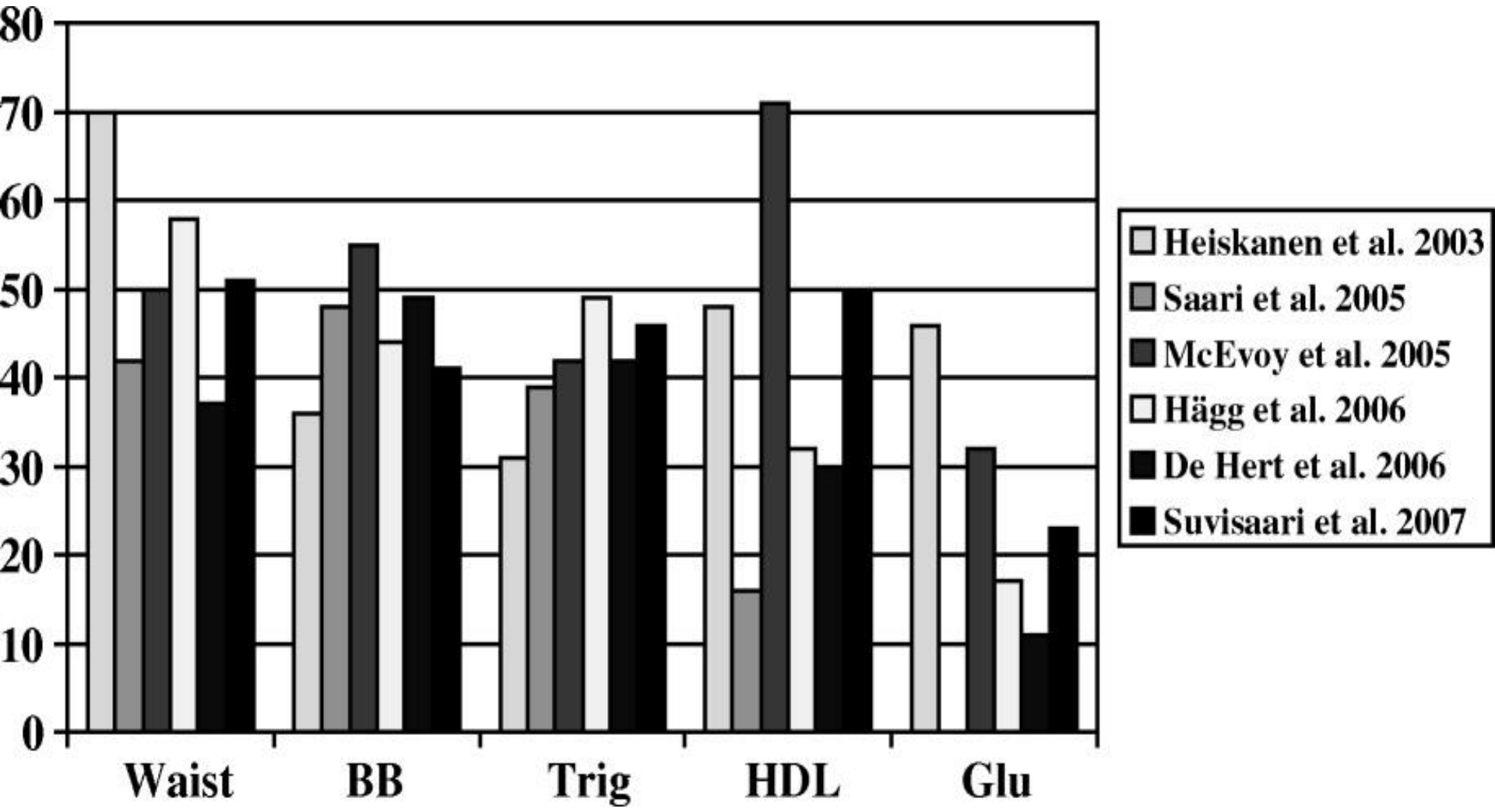
Novick D et al
Eur.Neuropsychopharmacol.2009;19(8):542-50



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Kaponen HJ et al (2010) WJBiolPsych 11(2) 262

DM & Sz

- Higher risk for CLZ than other APS
- More recent MA suggest RSP & OLZ, poss. QTP too
- Order of relative risk of 1.35, mostly in first 3/12
- Direct effect on glucose metabolism, not just weight effect

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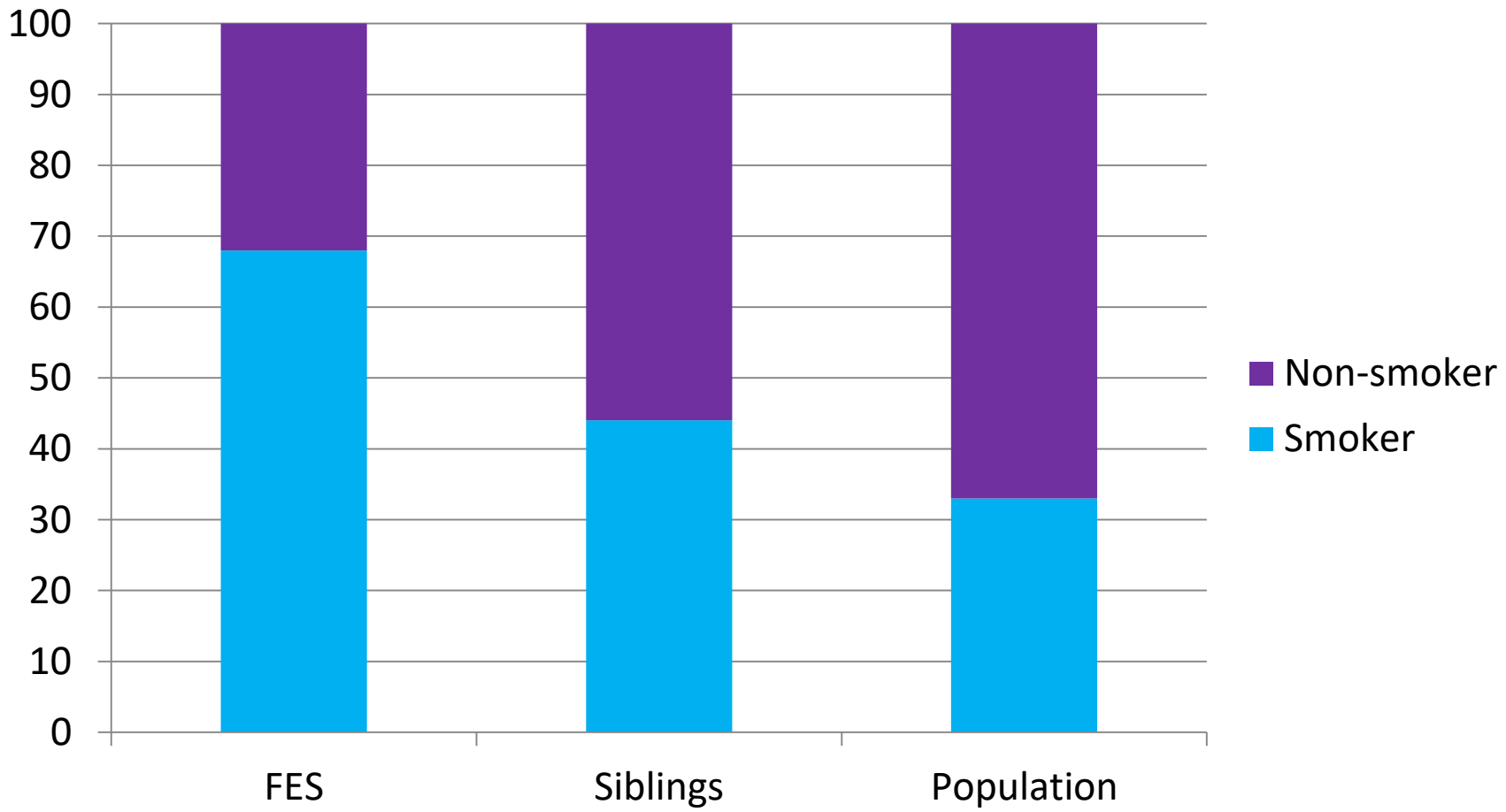
Citrome L et al (2007)
Annals of Pharmacoth 41;1593-1603

Smoking



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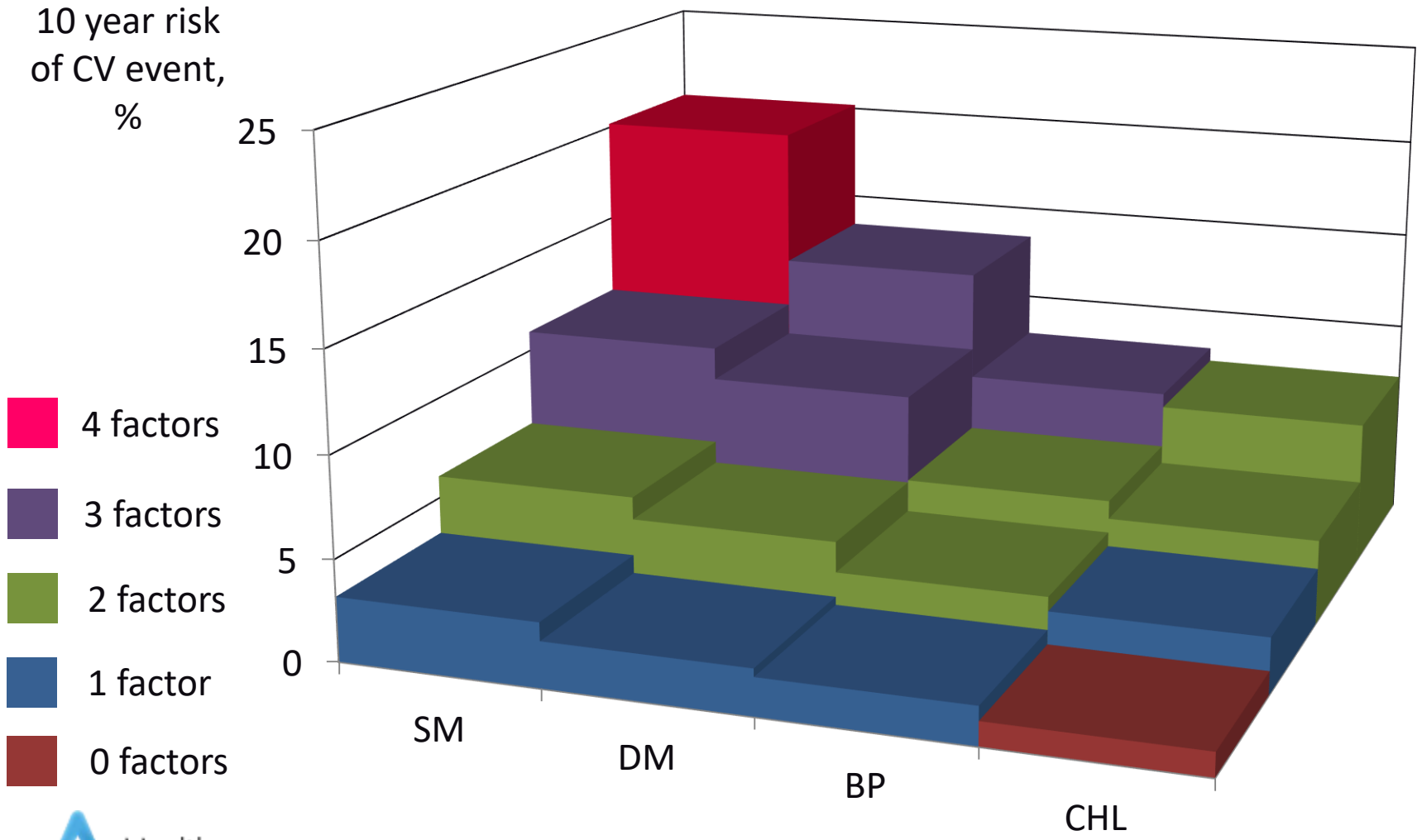
from Birtwhistle M, Drake RJ in prep.

Cardiovascular disease risk



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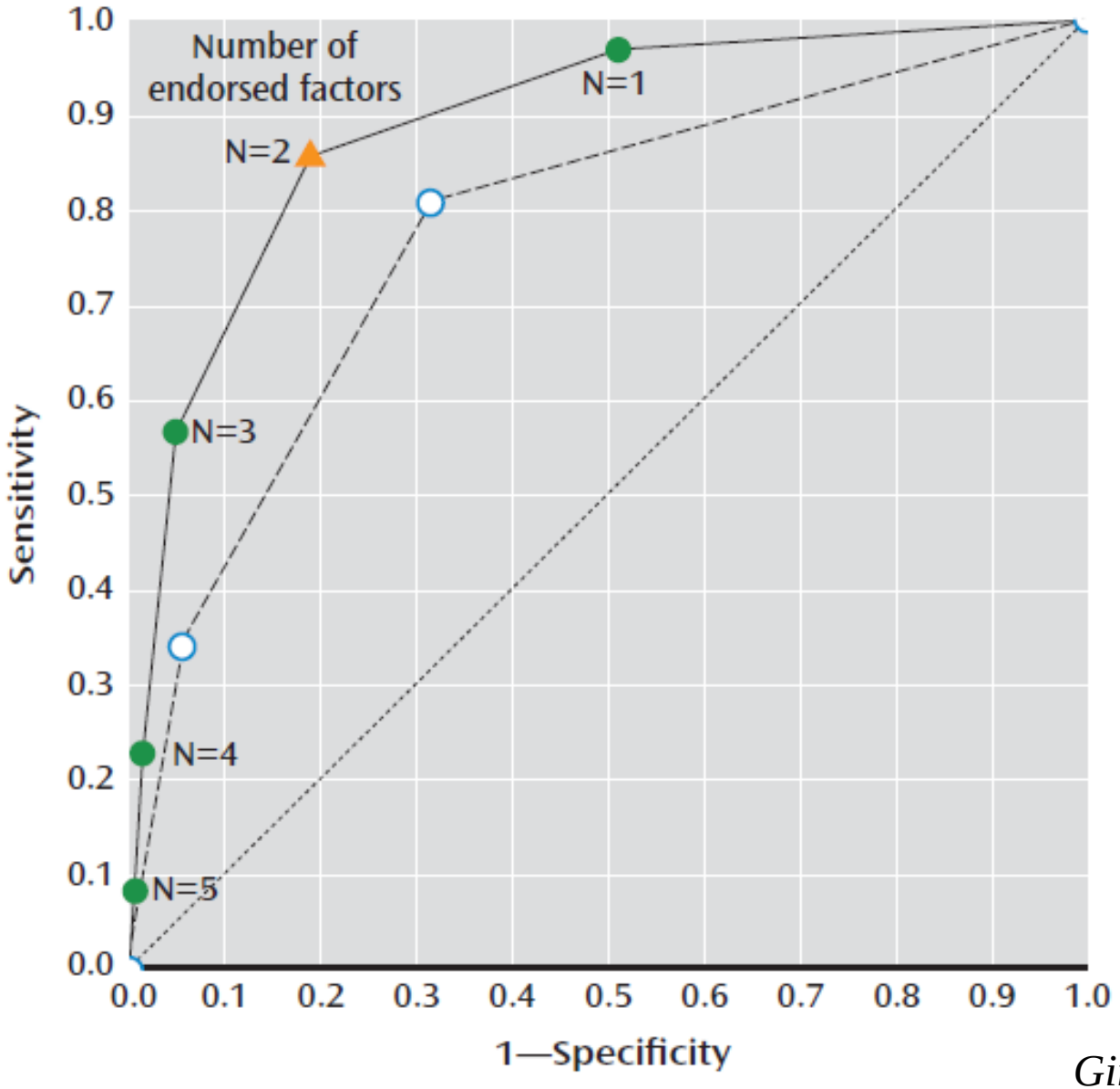
Plotted with data from American College of Cardiology
http://tools.cardiosource.org/ASCVD-Risk-Estimator/

FIGURE 2. Receiver Operating Characteristic Curves for Distinguishing Between Patients With Drug-Induced Long QT and Normal ECG[a]



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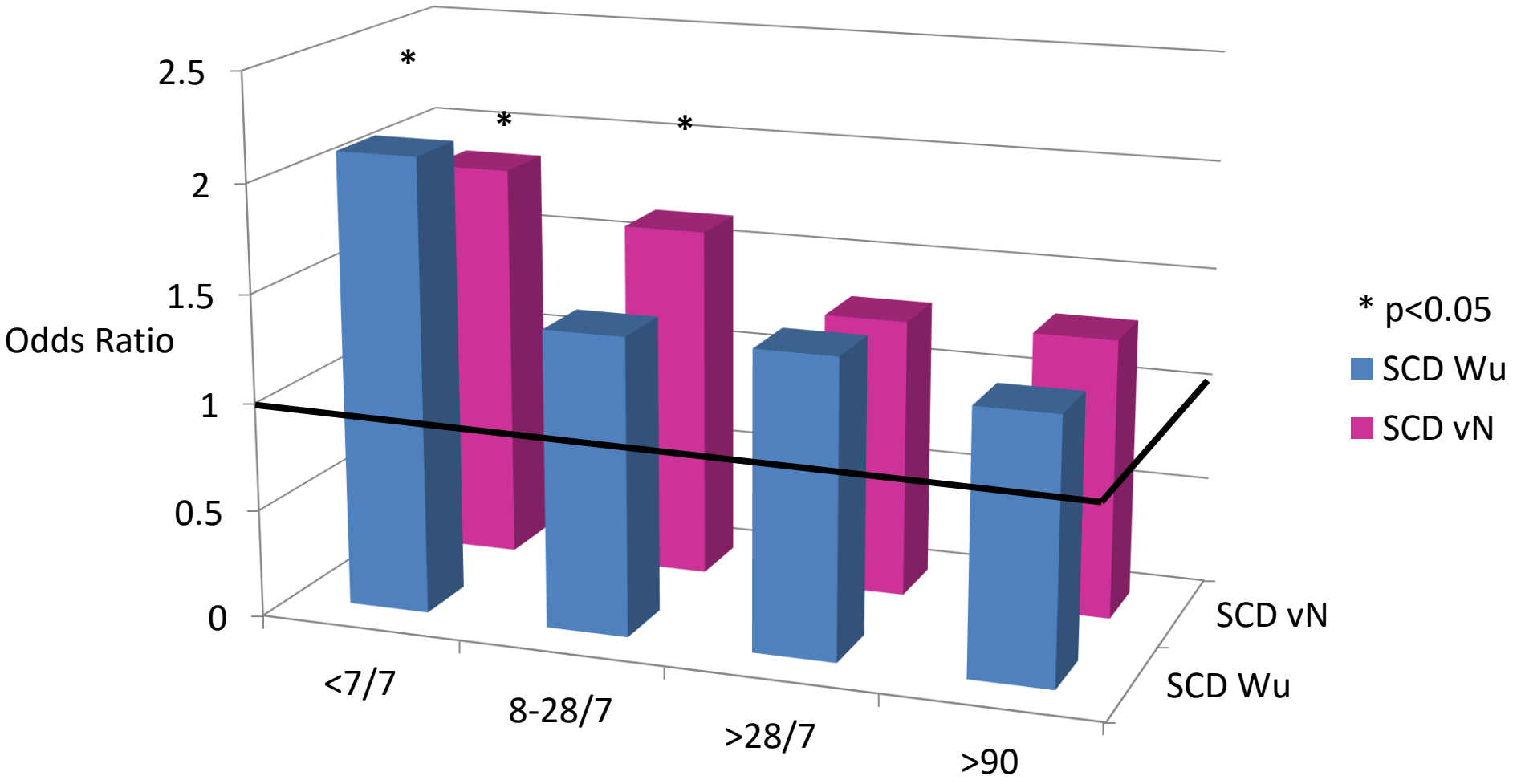
Girardin FR et al.
Am J Psychiatry 2013;170:1468-76

SCD by time



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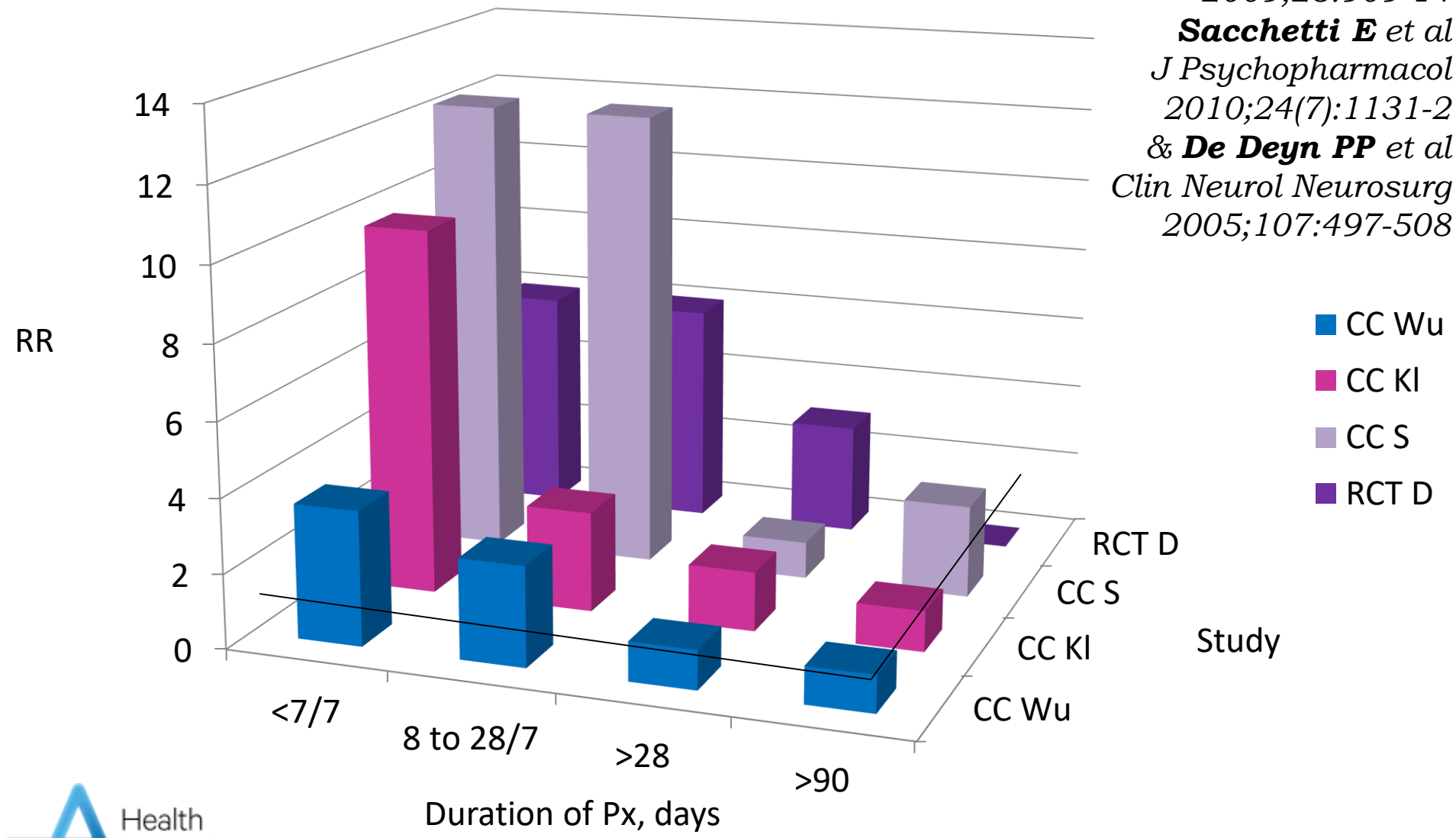
Plotted using data from ***Wu CS*** *et al. J Am Heart Assoc. 2015;4:e001568 & **van Noord C** et al. Heart 2011;97:215-20*

Plotted using data from ***Wu CS*** *et al Biol Psychiatr 2013;73:414-21*
Kleijer BC *et al J Psychopharmacol 2009;23:909-14*
Sacchetti E *et al J Psychopharmacol 2010;24(7):1131-2*
& ***De Deyn PP*** *et al Clin Neurol Neurosurg 2005;107:497-508*

CVA risk by time



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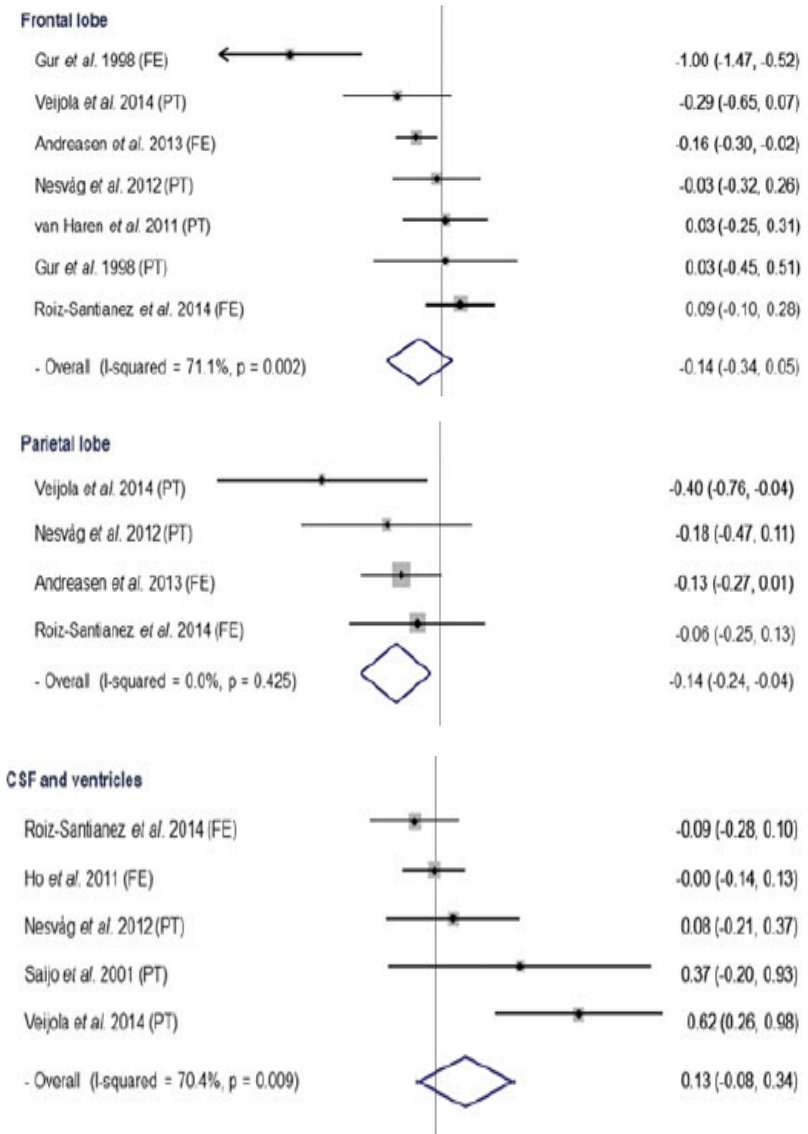
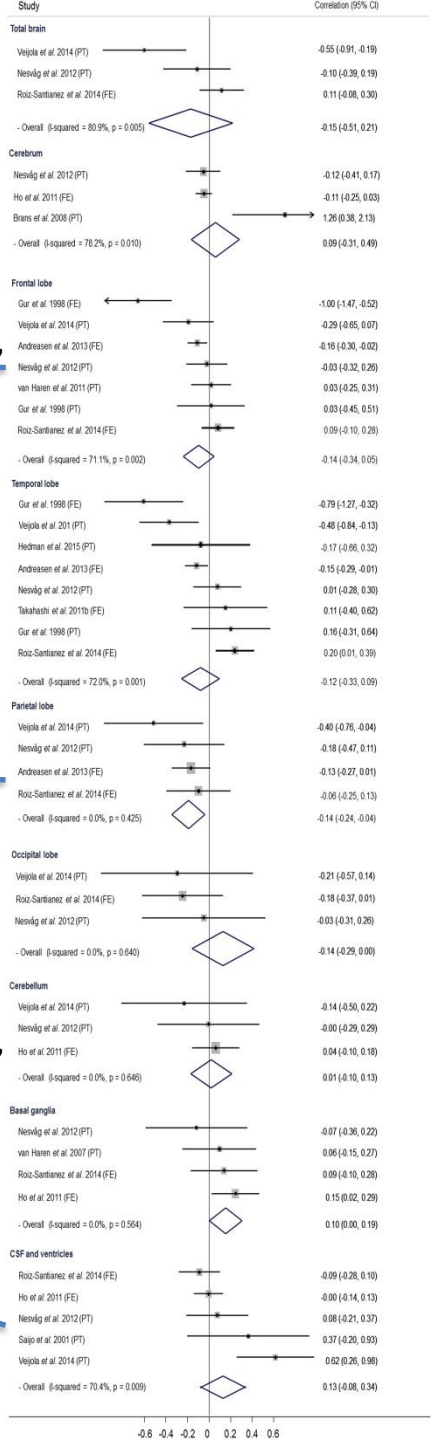
Forest plot of average study correlations between antipsychotic dose and volume change in CSF and ventricles, basal ganglia, frontal, temporal and parietal lobe. FE = first episode subjects, PT = previously treated subjects.



Not quite significant correlation, significant heterogeneity

Significant correlation, Non-significant heterogeneity

Not quite significant correlation, significant heterogeneity



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Hutaniska S et al.
Hum Psychopharmacol Clin Exp. 2017;32:e2574.

Efficacy

HOW WELL DO THEY WORK?

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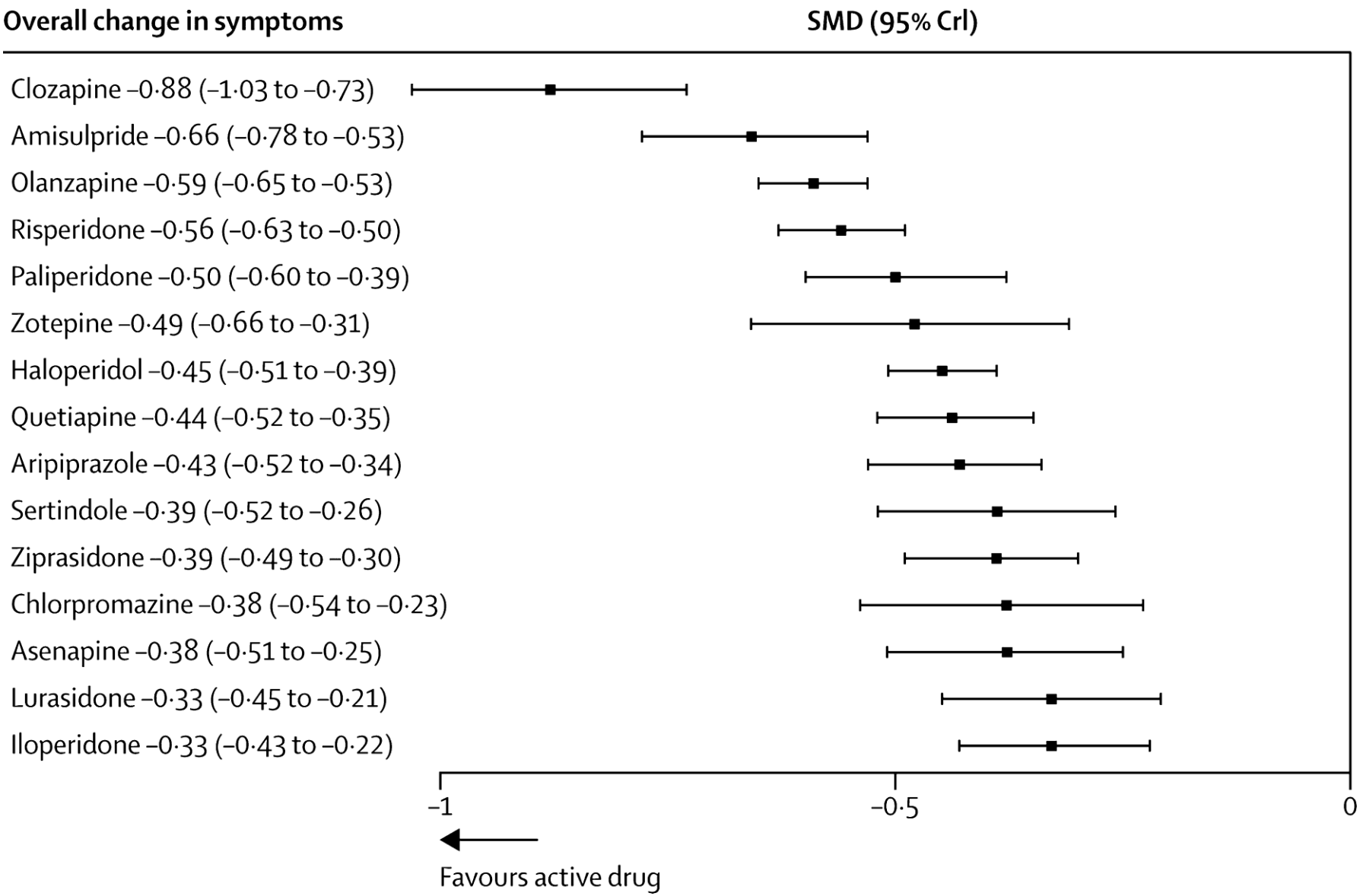

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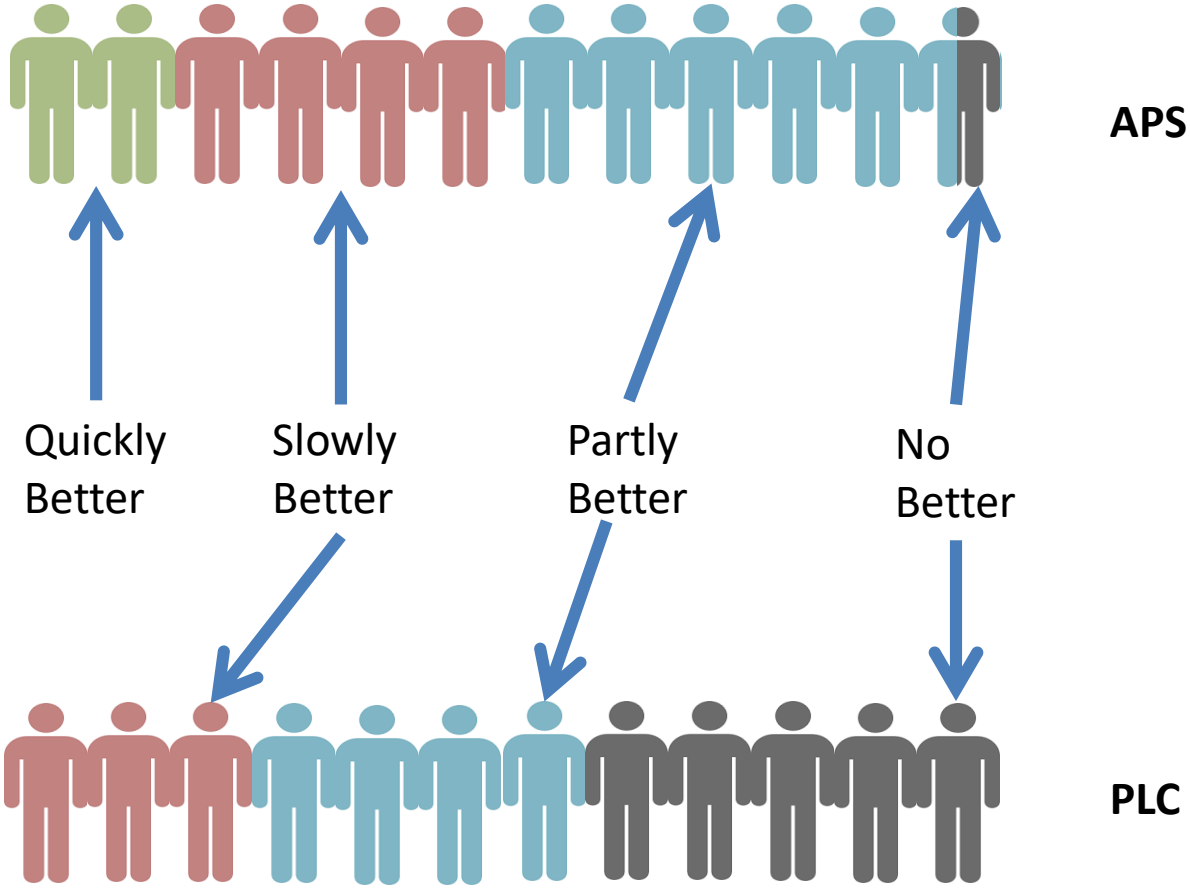
Leucht S et al. *Lancet* 2013;382(9896):951-62

Antipsychotics for relapse



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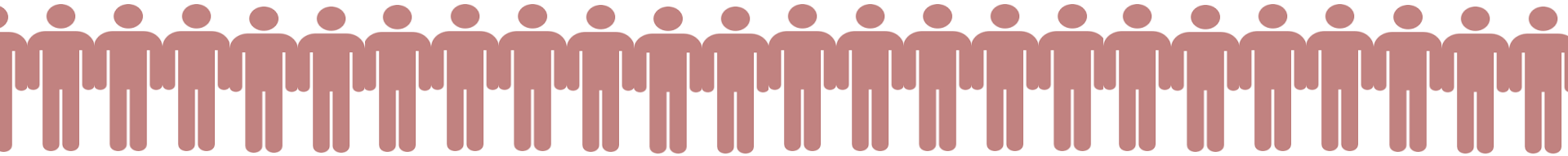
Marques TR et al. Psychological Medicine.2011;41:1481–1488

Antipsychotics v placebo to prevent relapse



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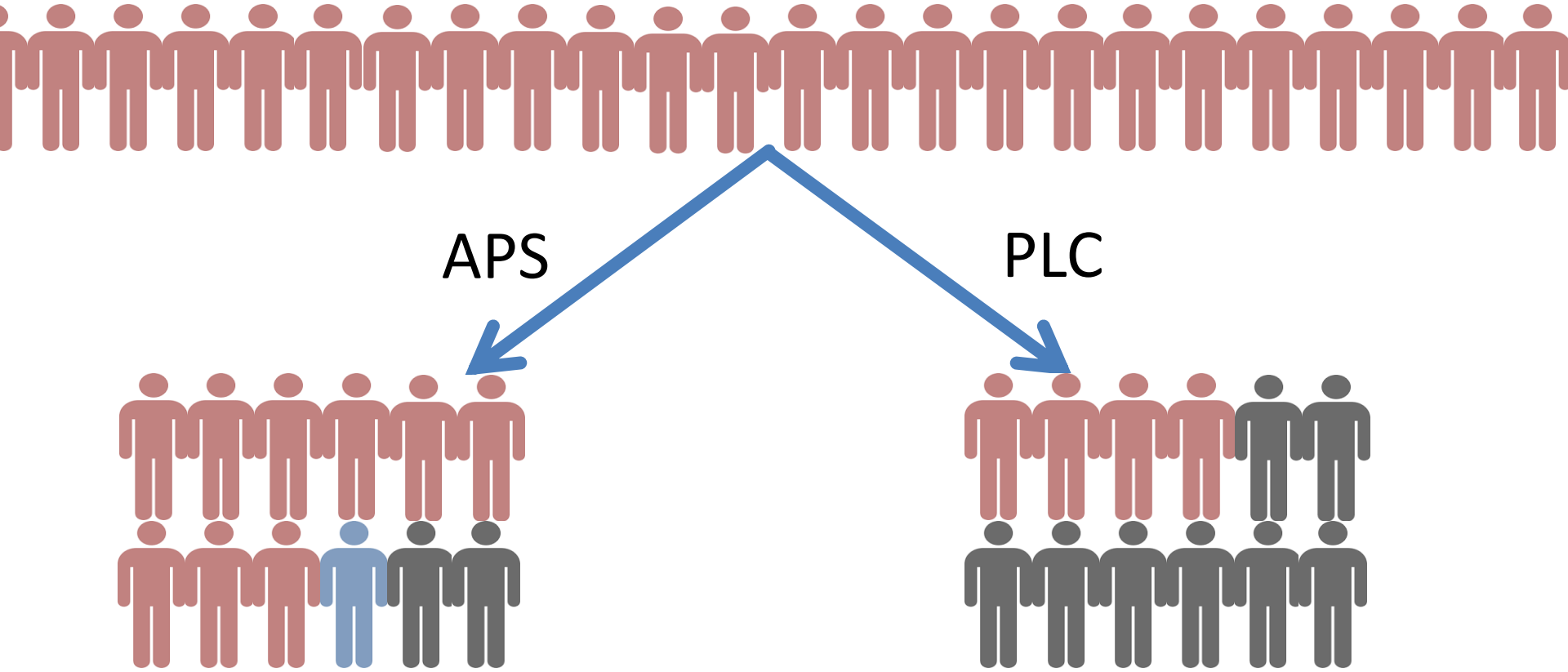
From Leucht S et al.,Lancet.2012;379:2063-71

Antipsychotics v placebo to prevent relapse



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from Leucht S et al.,Lancet.2012;379:2063-71

APS for Bipolar

- Mania:
  - HPL, RSP, OLZ probably most effective acute monotherapy; probably increase response to mood stabilisers about 1.5-fold
  - Relapse relative risk about 0.58 with OLZ, similar with QTP, RSP, ARP
- Depression:
  - QTP, OLZ+Fluox best; data not clear for RSP, ARP
  - SGA probably better than FGA for prophylaxis

Smith LA et al. *Acta Psychiatr Scand* 2007: 115: 12–20
Smith LA et al. *Bipolar Disord.* 2007; 9: 394-412
Lindstrom L et al. *J Affective Disorders* 2017;213:138-70

Effectiveness

HOW WELL DO THEY WORK?

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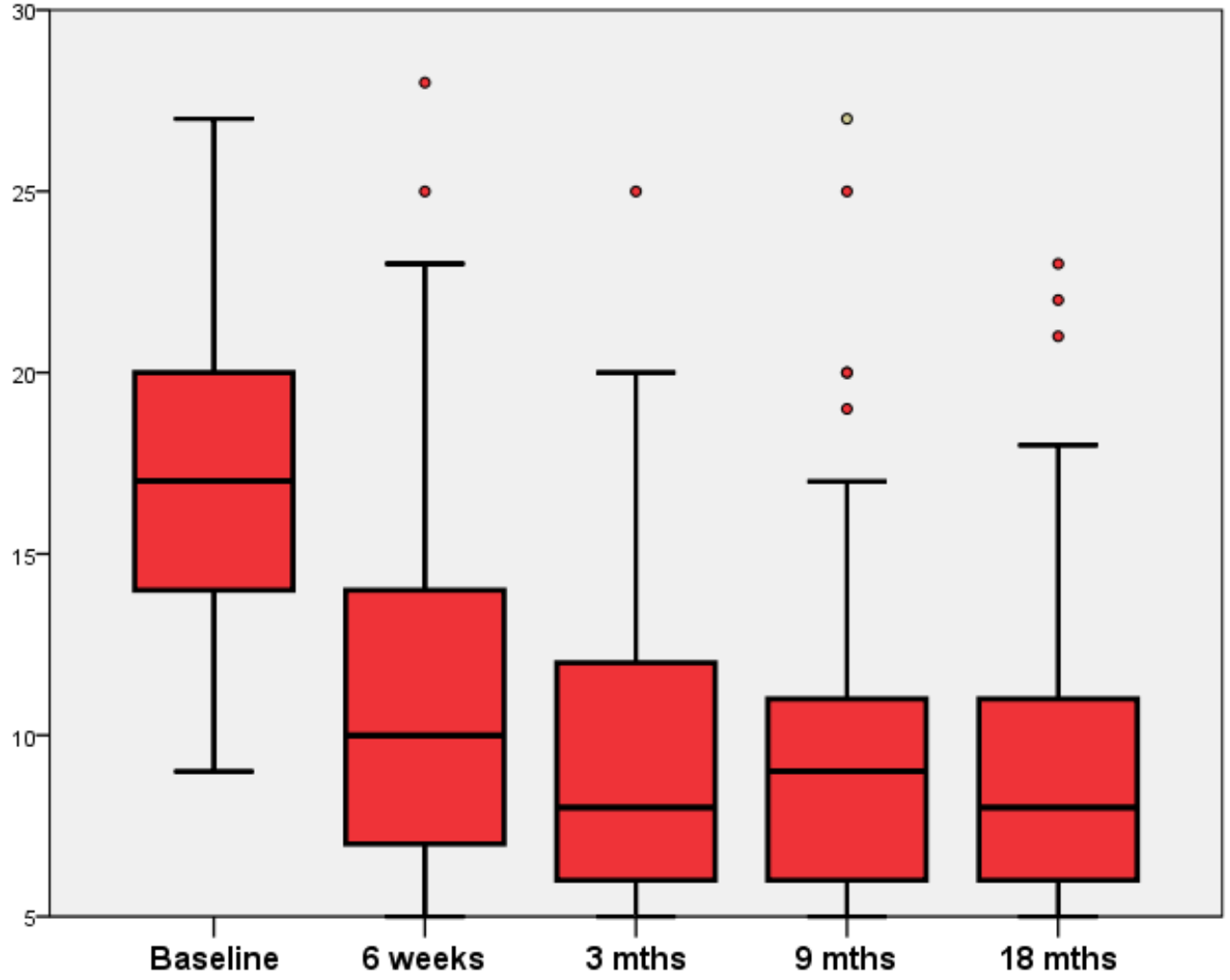
Psychotic symptoms after first presentation



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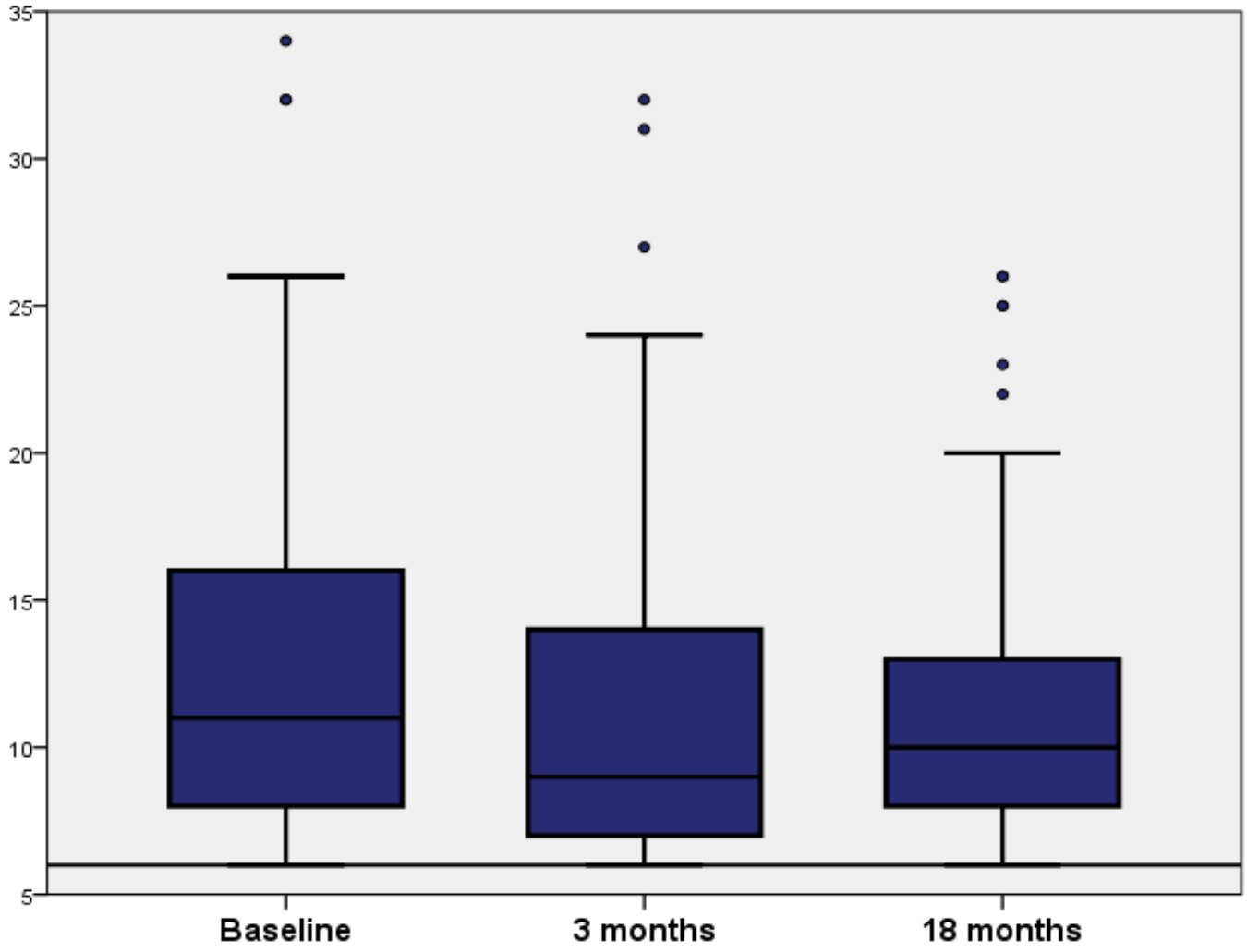
Negative symptoms after first presentation



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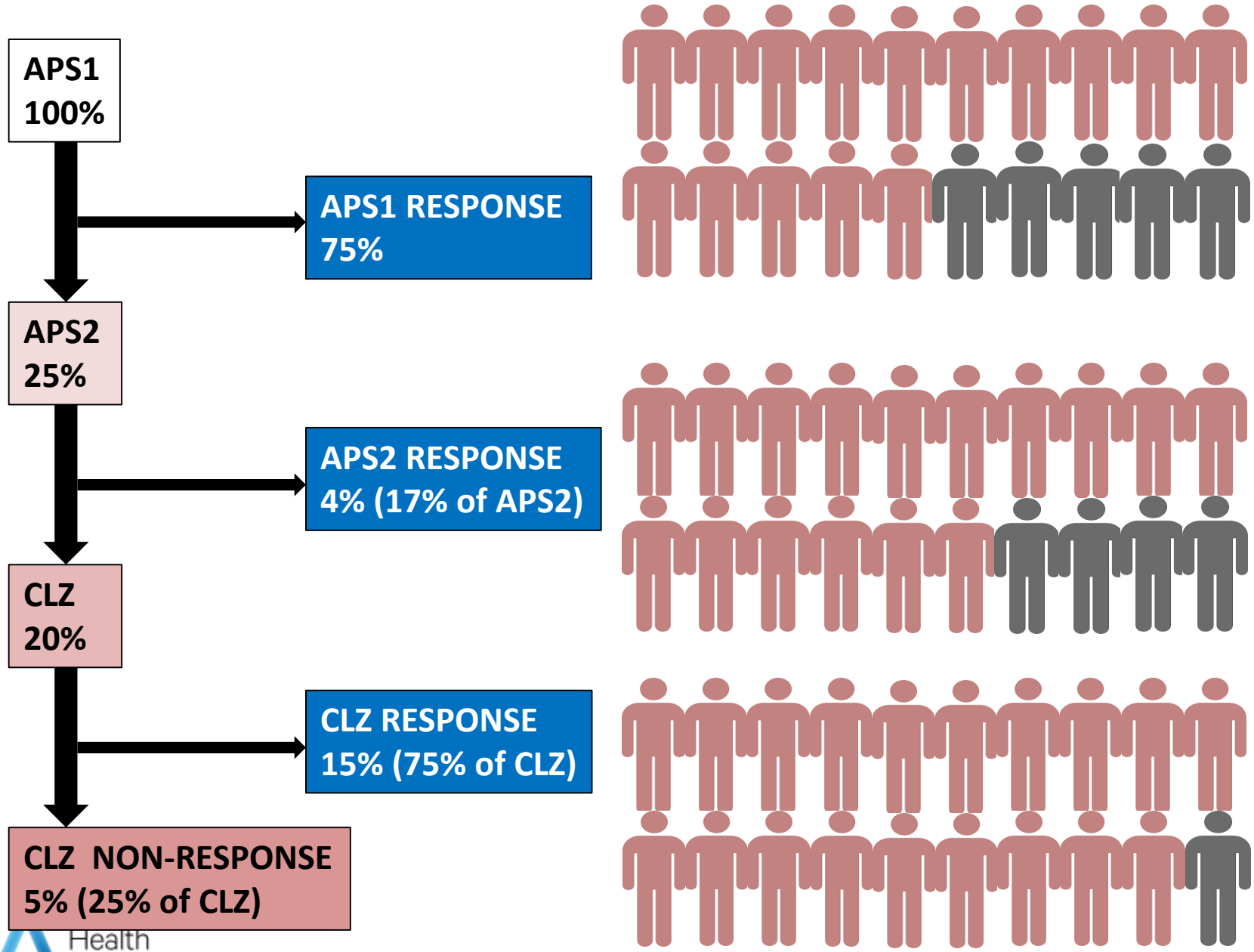

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Agid O et al.J Clin Psych 2011; 72 (11): 1439

APS1
100%

APS1 RESPONSE
75%

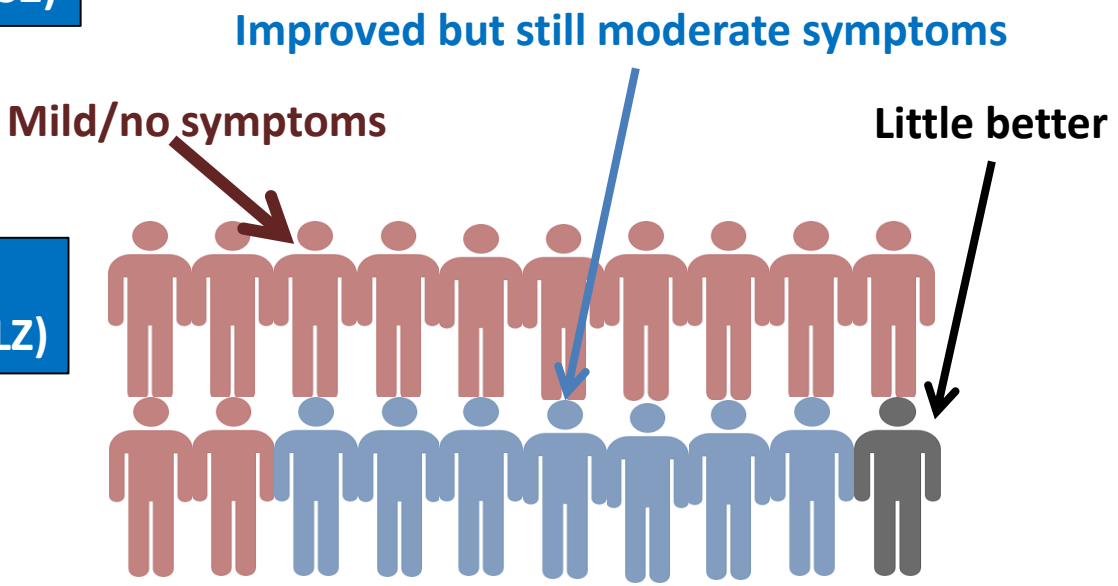
APS2
25%

APS2 RESPONSE
4% (17% of APS2)

CLZ
20%

CLZ RESPONSE
15% (75% of CLZ)

CLZ NON-RESPONSE
5% (25% of CLZ)



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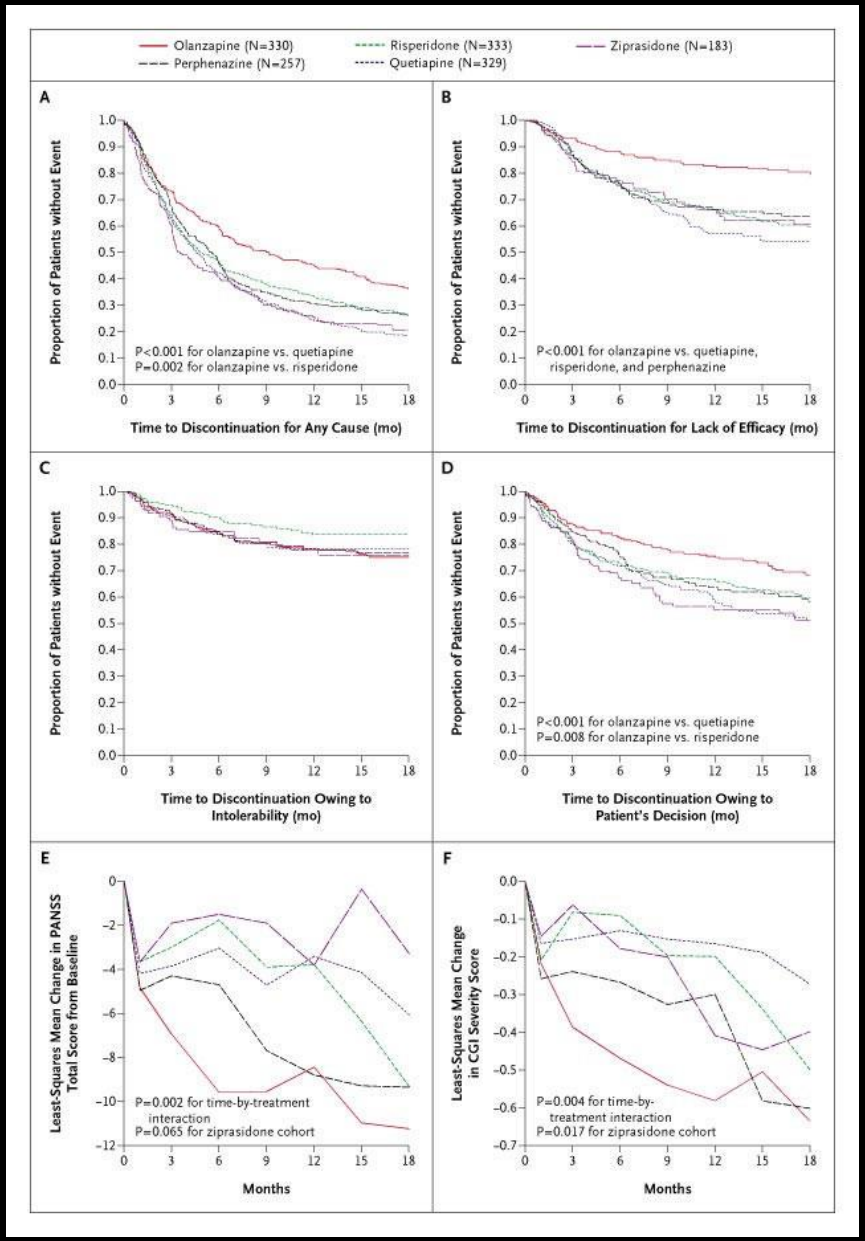
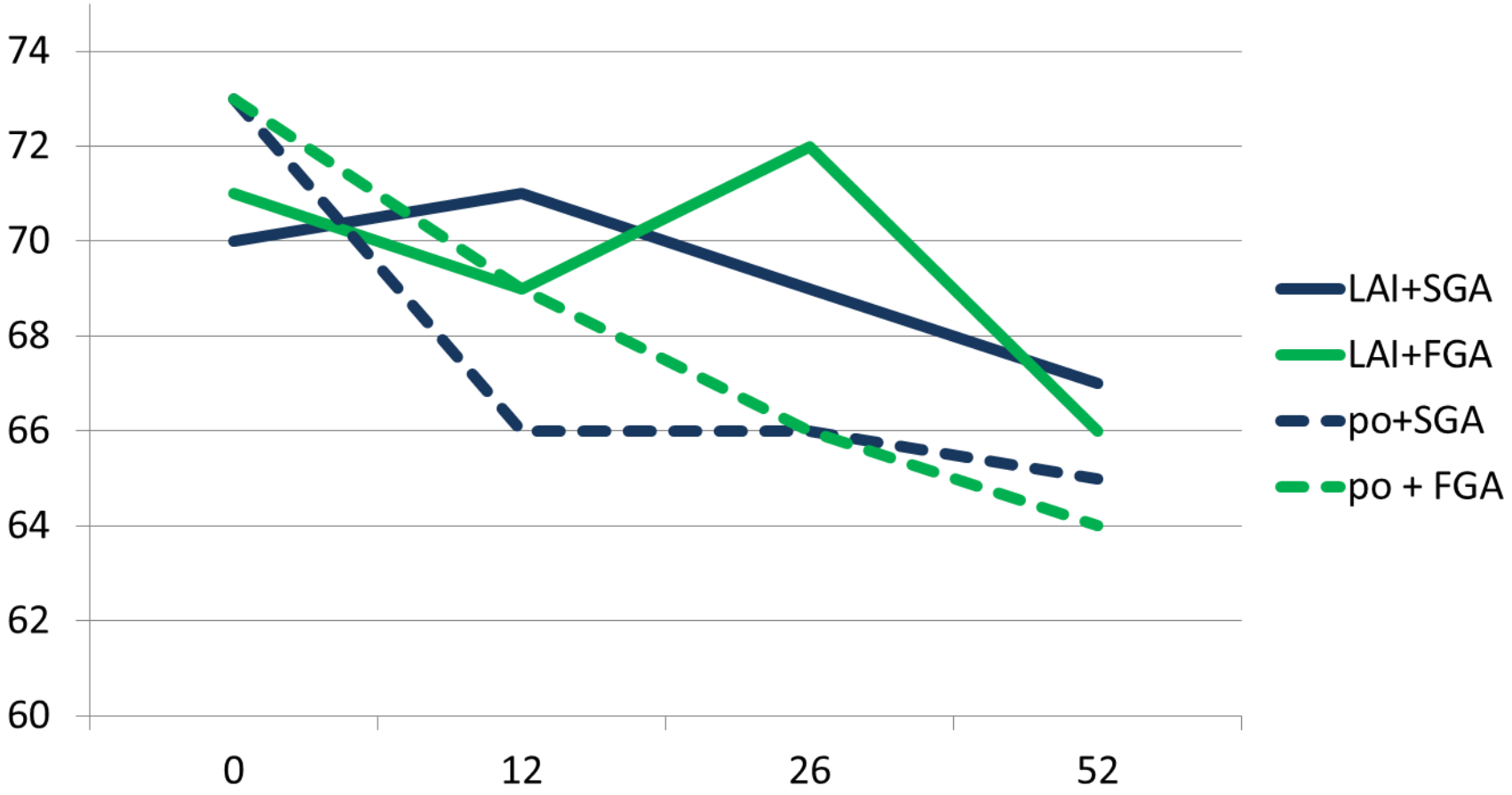
Agid O et al.J Clin Psych 2011; 72 (11): 1439



Lieberman JA et al. *N Engl J Med* 2005;353:1209-1223.

CUTLASS 1: PANSS v weeks



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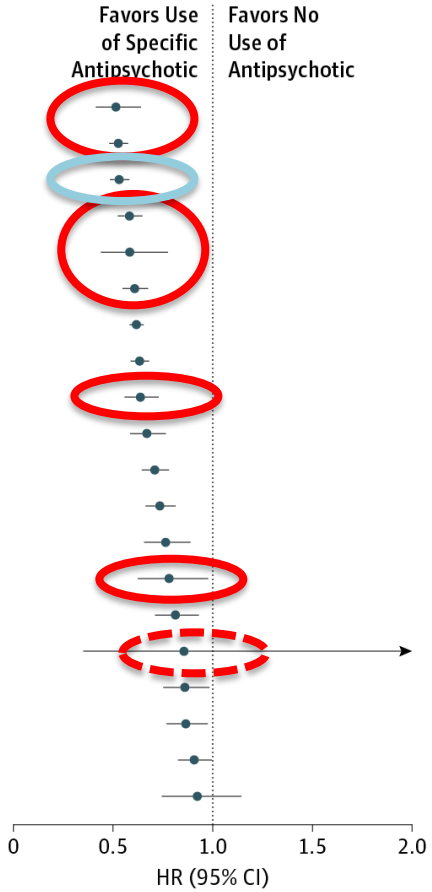
cf Barnes TRE et al. BJPsych 2013;203:215-220

Hold on, effectiveness does differ

Treatment	HR (95% CI)
LAI paliperidone	0.51 (0.41-0.64)
LAI zuclopenthixol	0.53 (0.48-0.57)
Oral clozapine	0.53 (0.48-0.58)
LAI perphenazine	0.58 (0.52-0.65)
LAI olanzapine	0.58 (0.44-0.77)
LAI risperidone	0.61 (0.55-0.68)
Polytherapy	0.62 (0.58-0.65)
Oral olanzapine	0.63 (0.59-0.68)
LAI haloperidol	0.64 (0.56-0.73)
Oral zuclopenthixol	0.67 (0.59-0.76)
Oral risperidone	0.71 (0.64-0.78)
Oral aripiprazole	0.73 (0.66-0.81)
Oral levomepromazine	0.76 (0.66-0.89)
LAI flupentixol	0.78 (0.62-0.98)
Oral haloperidol	0.81 (0.71-0.93)
LAI fluphenazine	0.86 (0.35-2.08)
Other oral formulations	0.86 (0.75-0.98)
Oral perphenazine	0.86 (0.77-0.97)
Oral quetiapine	0.91 (0.83-1.00)
Oral flupentixol	0.92 (0.74-1.14)



Hazard Ratio for hospitalisation, compared to no antipsychotic, after starting antipsychotics in Sweden (2006-14; N=29,823)

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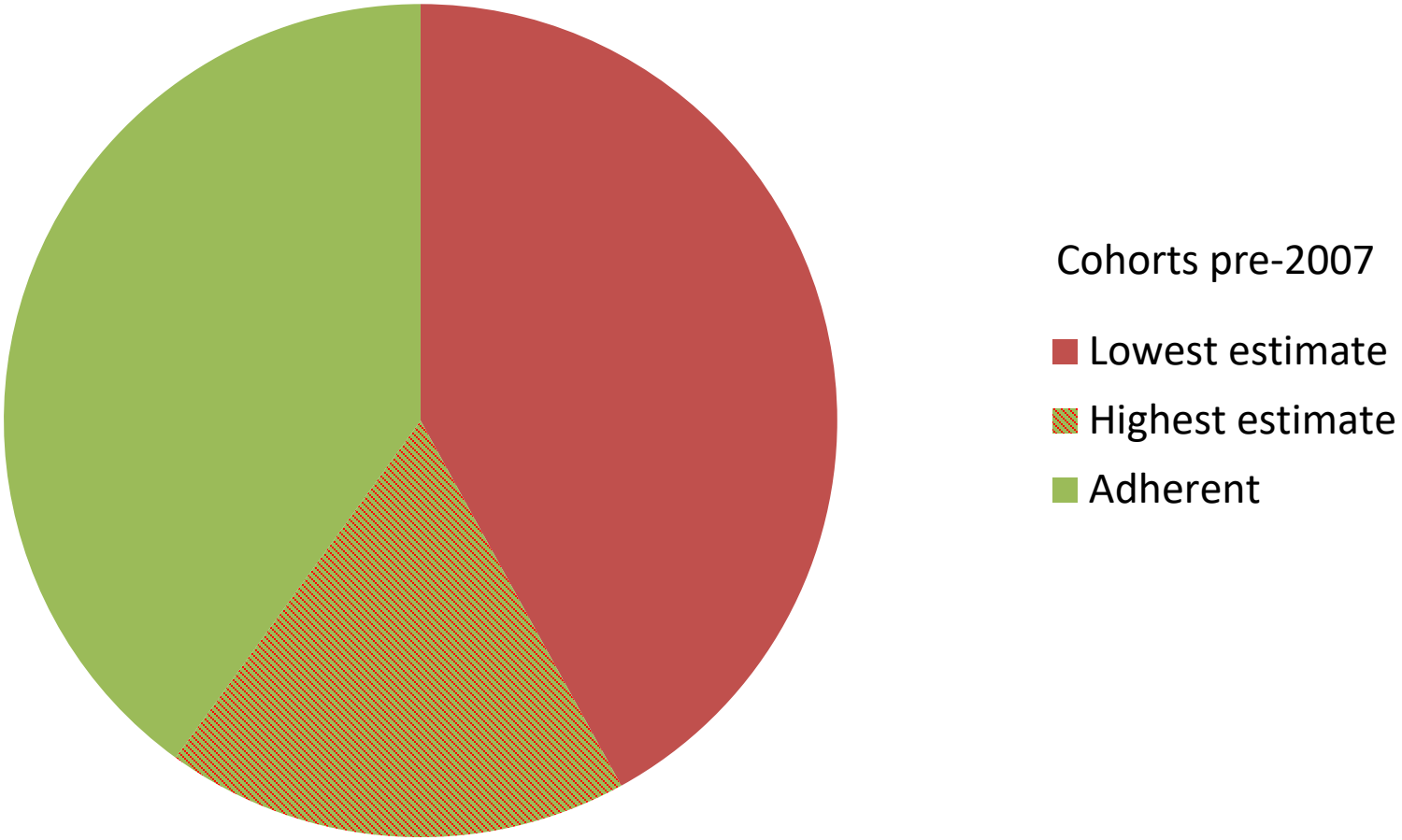
Tiihonen J et al. *JAMA Psychiatry*.2017;74(7):686-693

Stop Meds in first 1-5yrs



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See *Drake RJ et al. Schizophr Bull. 2015;41(3):584-96.*

WHEN AND HOW CAN WE STOP ANTIPSYCHOTICS?

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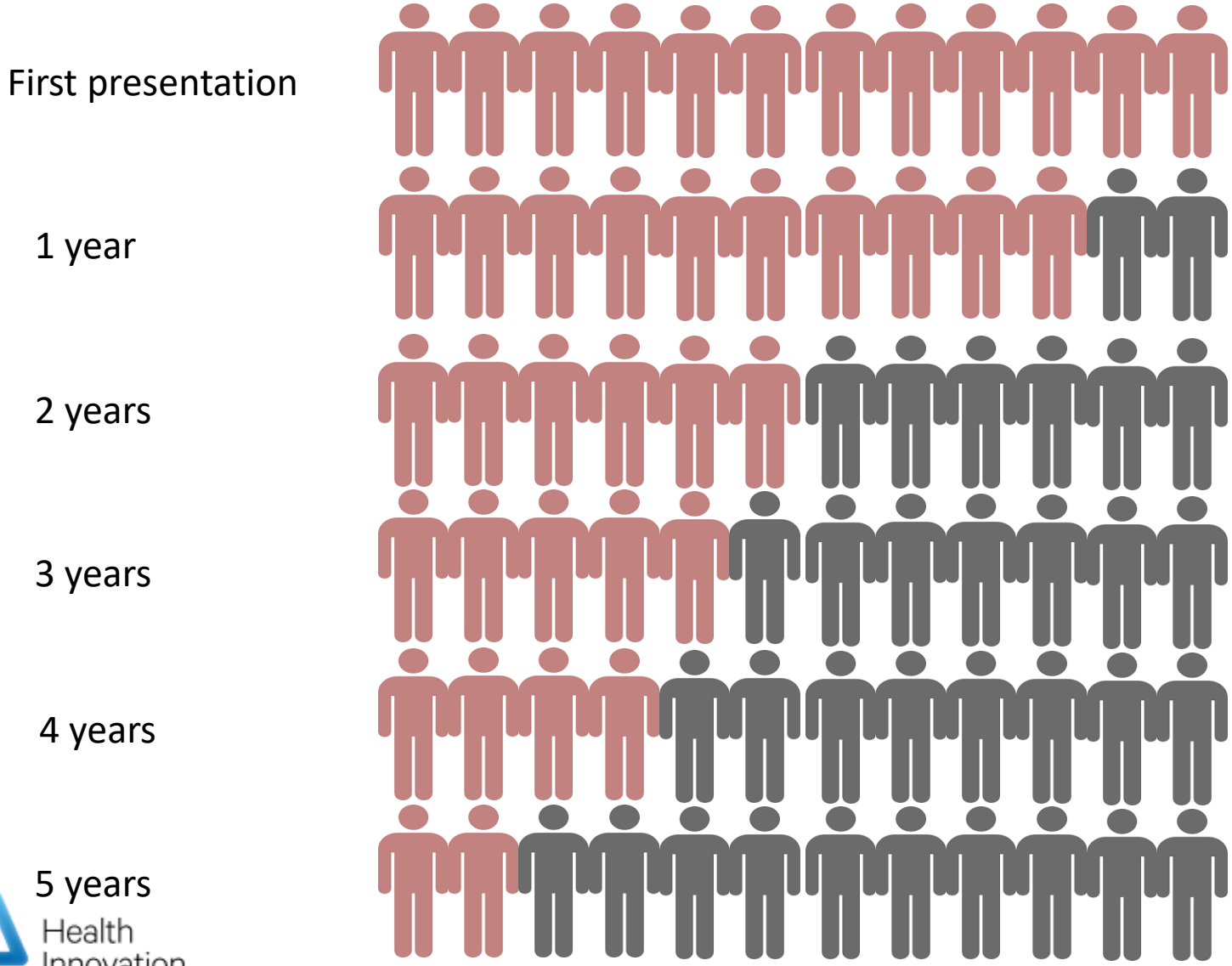
After first episodes



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From Robinson D et al, ArchGenPsych.1999;56:241-7

From Wunderink L et al JAMAPsych.2013;70(9):913-30

Discontinuing after first episodes

18 months

Stay off Stop & relapse On APS Relapse on APS

7 years

Stay off Low dose Full dose

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Summary

- All D2 receptor antagonists with differing adverse effect profiles
- Efficacy greatest for CLZ
- Drivers of effectiveness: LAI, CLZ, right choice
- Efficacious for mania as monotherapy or adjunctive; but apart from QTP and OLZ + Fluox less clear for bipolar depression

EXERCISES

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First episode

- 23 male U/E presents with delusions, hallucinations, thought disorder
  - for 2 weeks after abrupt onset
  - not depressed/excited, not suicidal, no ideas threat
- What treatment? What dose? When?
- If responds but not remitted, what to do?

TRS

- Same person but failed to respond after 12 months to OLZ & PPD LAI, limited benefit CBTp & no FI available
- What to do?
- Why is it relevant that he's a non-smoker?

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