European College of Neuropsychopharmacology



ANTIPSYCHOTICS: Clinical Pharmacology Celso Arango carango@hggm.es



Centro de Investigación Biomédica En Red de Salud Mental www.hggm.es/ua

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ecnp

🚾 Comunidad de Madrid

Pre-Lecture Test Question 1

- 1. Which of the following is an antipsychotic dose that is in excess of the optimal?
 - A. Aripiprazole 15 mg/day
 - B. Ziprasidone 80 mg bid
 - C. Haloperidol 20 mg qd
 - D. Risperidone 4 mg/day
 - E. Quetiapine 300 mg bid

- 2. Which of the following antipsychotics must be taken with food in order to prevent significant loss of absorption?
 - A. Ziprasidone
 - B. Olanzapine
 - C. Clozapine
 - D. Aripiprazole
 - E. Risperidone

- 3. Which of the following is the recommended starting dose for clozapine?
 - A. 25 mg twice a day
 - B. 12.5 mg
 - C. 25 mg
 - D. 50 mg

- 4. All of the following are true of a patient on risperidone who gets parkinsonian side effects, except:
 - A. D2 receptor occupancy is 75% or more
 - B. The patient is above the "neuroleptic threshold"
 - C. Patient is at risk for secondary negative symptoms
 - D. Raising the dose is likely to be helpful

- 5. What is the drug of choice for a schizophrenia patient with polydispia?
 - A. Olanzapine
 - B. Thirodazine
 - C. Ziprasidone
 - D. Pimozide
 - E. Clozapine

The NNT for antipsychotics is lower for

- A. Schizophrenia
- B. Schizoaffective disorder
- C. Bipolar disorder
- D. Aggressive behaviour in autism
- E. Depression

Which one of these antipsychotics has a longer half life?:

- A. Olanzapine
- B. Haloperidol
- C. Chlorpromazine
- D. Aripiprazole
- E. Quetiapine

Which one of these antipsychotics is the only one that does not have affinity for the D2 receptor?

- A. Paliperidone
- B. Quetiapine
- C. Chrlopromazine
- D. Aripiprazole
- E. None

- When do we have plasma levels similar to oral risperidone with Risperidone consta (25 mg)
 - A. Day 1
 - B. Day 5
 - C. Day 10
 - D. Day 15
 - E. Day 30

What antipsychotic would you not recommend for a 16 year old with a first psychotic episode

- A. Aripiprazole
- B. Risperidone
- C. Quetiapine
- D. Olanzapine
- E. Haloperidol (low dose)

- For what drug do guidelines (e.g PORT) recommend to measure plasma levels (therapeutic window)?
 - A. Aripiprazole
 - B. Clozapine
 - C. Quetiapine
 - D. Olanzapine
 - E. Haloperidol

- Most of the weight gain with antipsychotics takes place in:
 - A. First month
 - B. 3 months
 - C. 6 months
 - D. 1 year
 - E. 2 years

The half life of LAI (depot) antipsychotics is:

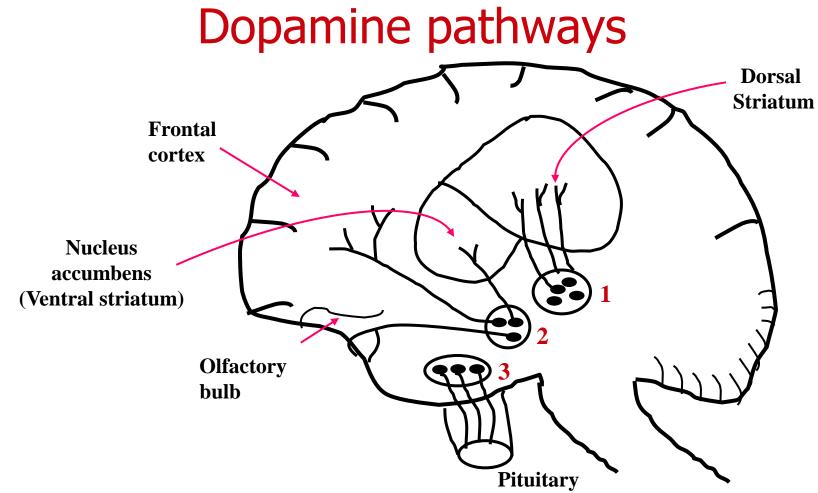
- A. 2 weeks
- B. 4 weeks
- C. 12 weeks
- D. A and B are correct
- E. A, B and C are correct

Outline of Lecture

- Introduction
- Algorithm for selecting antipsychotics
- What do they treat and what they do not treat
- Most common antipsychotics: minimal facts we should know about them
- Efficacy
- Safety and tolerability

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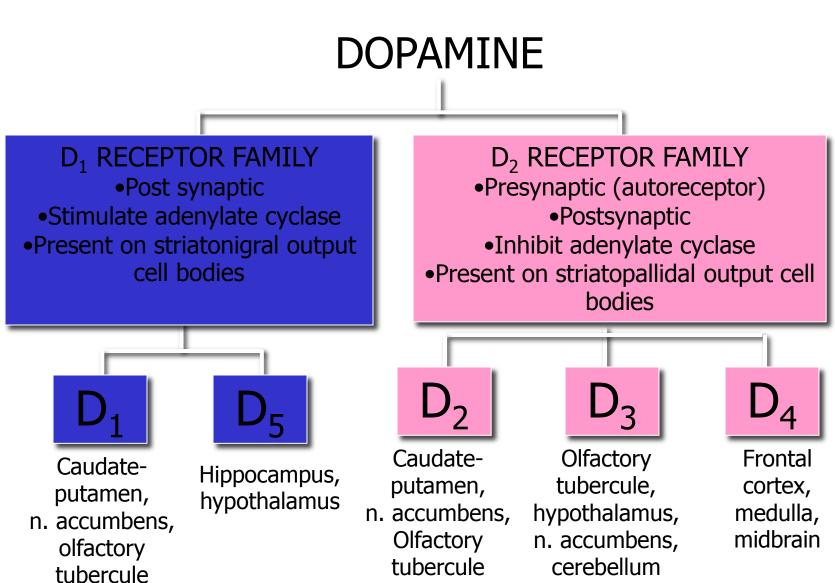


1. Nigrostriatal pathway (substantia nigra)

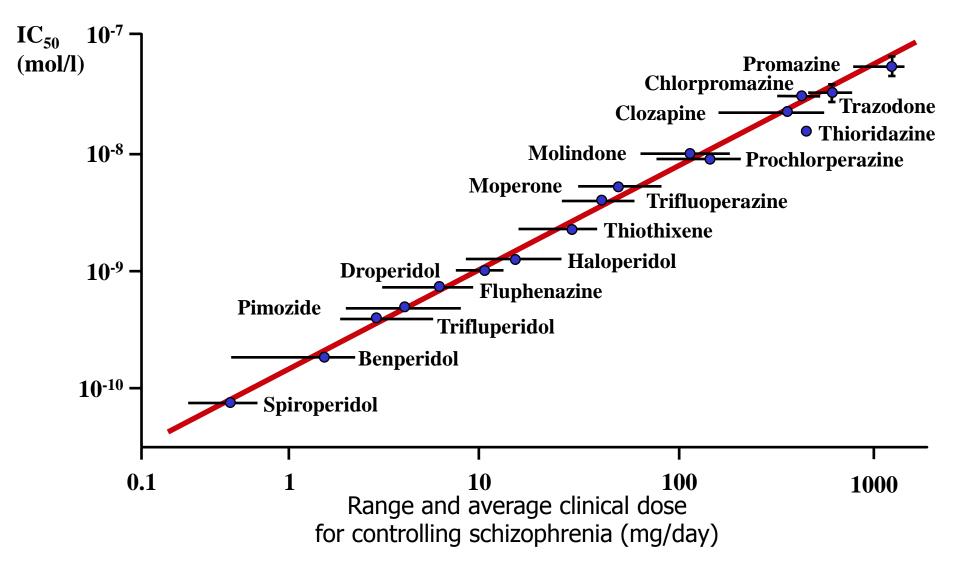
Parkinson's disease, initiation of motor plans

- 2. Mesocortical and mesolimbic pathways (Ventral tegmental area: VTA) Psychosis, reward and motivation
- 3. Tuberoinfundibular pathway (Median eminence) Prolactin release

CLASSIFICATION OF DOPAMINE RECEPTORS



AFFINITY FOR D₂ RECEPTORS & CLINICAL POTENCY









Barriers to Drug Discovery: Reasons for Minimal Progress since 1952

Adherence to single disease paradigm where psychosis represents the latent disease structure.

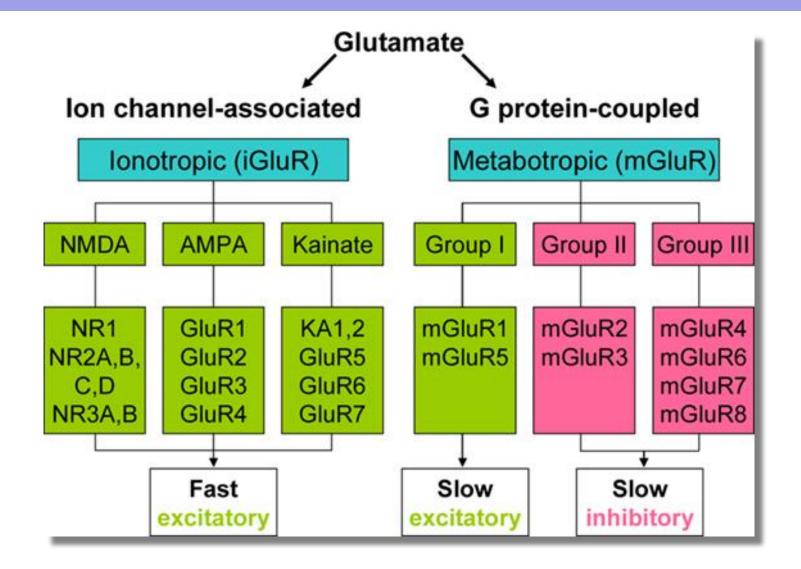
Discovery platforms produce dopamine antagonists.







CLASSIFICATION GLUTAMATERGIC RECEPTORS



Glutamatergic neurotransmission modulators under evaluation for schizophrenia treatment

NMDA receptor

Glycine site full agonists (glycine, D-serine, D-alanine) Glycine site partial agonists (D-cycloserine) Glycine type I transporter inhibitors (N-methylglycine, Bitopertin:negative studies, AMGEN: stopped) D-serine transport inhibitors

AMPA receptor

Positive allosteric modulators (AMPAkines)

Metabotropic receptors

mGluR_{2/3} activators (N-acetylcysteine) mGluR_{2/3} agonists (Pomaglumetad: failed)

CONVENTIONAL ANTIPSYCHOTICS

Classification: Chemical type Representative drug

Phenothiazines Aliphatic chlorpromazine Piperidine thioridazine Piperazine trifluoperazine Thioxanthines flupenthixol Butyrophenones haloperidol Diphenylbutylpiperidines *pimozide* Dibenzoxapines sulpiride Indoles oxypertine

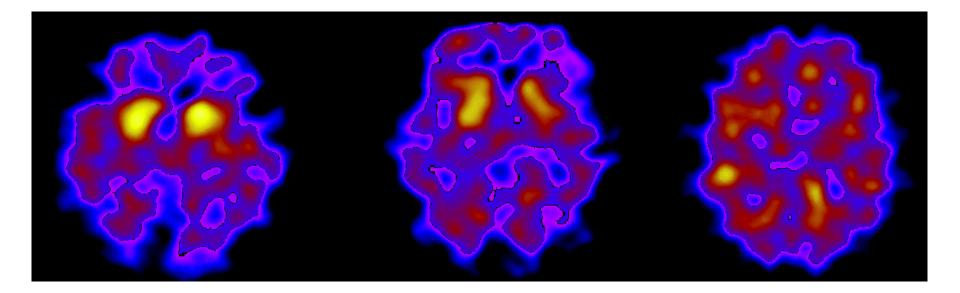
NEW ANTIPSYCHOTICS

Classification: Chemical type Representative drug

Dibenzazepines

Dibenzodiazepine Thienobenzodiazepine Dibenzothiazepine Benzisoxazoles Benzamides Benzisothlazoylpiperazines Imidazolidinone NNN

clozapine olanzapine quetiapine risperidone amisulpride ziprasidone sertindole asenapine

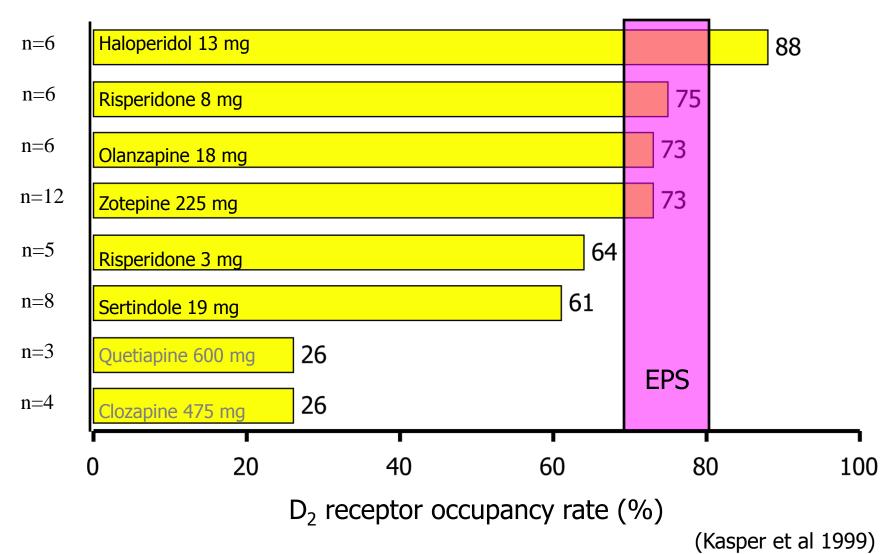


Healthy Volunteer

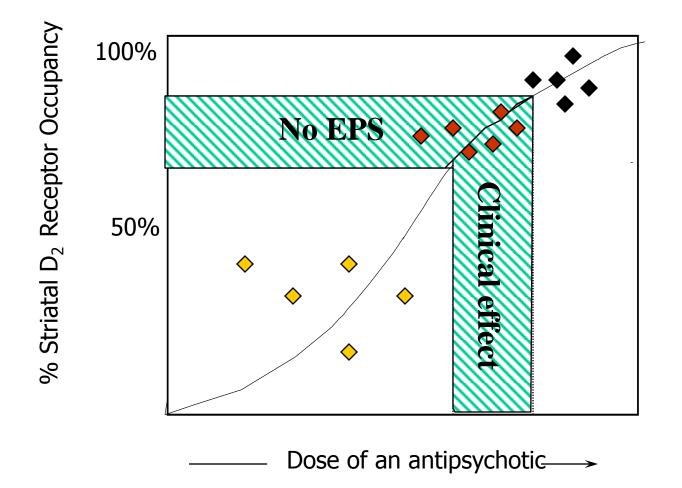
Clozapine treated Schizophrenia patient Typical antipsychotic treated schizophrenia patient

¹²³I-IBZM SPET scans of striatal D₂ receptor occupancy (Pilowsky et al 1992)

CONVENTIONAL & NEW ANTIPSYCHOTICS Striatal D₂ receptor occupancy rates



RELATIONSHIP BETWEEN D₂ RECEPTOR OCCUPANCY, EPS AND RESPONSE



(after, Farde et al, 1992, Nyberg et al 1996, Pickar et al 1996 & Kapur et al 2000)

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Initial challenge: diagnosis Potential psychotic disorders

- Schizophrenia
- Schizophreniform disorder
- Schizoaffective disorder
- Bipolar disorder
- Psychotic depression
- Brief psychotic disorder
- Psychotic disorder due to general medical condition
- Substance-induced psychotic disorder

- Post-psychotic depressive disorder of schizophrenia
- Delusional disorder
- Simple deteriorative disorder (simple schizophrenia)
- Shared psychotic disorder
- Postpartum psychosis
- Culture-bound psychotic syndromes
- Atypical psychotic disorders

Basic Algorithm For Selection of Antipsychotics

- Begin with antipsychotic that causes the less side effects or no side effects feared by **the patient you are treated**
- If patient had 4-6 week trial with full dose, but response unsatisfactory, try another antipsychotic
- If patient intolerant/unable to complete trial of initial agent, try another and then another until you get an adequate trial
- If treatment resistant positive symptoms after 2 adequate monotherapy trials try clozapine

CAUTION!! PROBLEMS WITH GENEREZABILITY

Males82%Mean age (years)37Age of onset (years)22>6 hospitalisations65%

Characteristics of patients participating in pivotal trials of new antipsychotics

Antipsychotics dosing

- Chinese and other East Asian ethnic individuals (and many Africans) usually need somewhat lower doses of antipsychotics metabolized by 2D6.
- 35-50% have a less active form of the 2D6 enzyme, rendering them "Slow Metabolizers" (SM's)

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PSYCHOSIS AND FEVER

There are other things besides positive symptoms!!

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

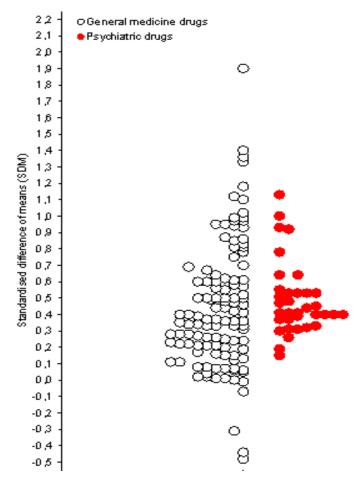
Stefan Leucht, Magdolna Tardy, Katja Komossa, Stephan Heres, Werner Kissling, Georgia Salanti, John M Davis

- 65 included randomised controlled trials with 6,493 patients
- Patients with schizophrenia, stabilised on antipsychotic drugs
- Published over long period, 1959–2011
- Any antipsychotic drug versus placebo (antipsychotics continued or withdrawn)
- 63 double-blind, 2 open randomised controlled trials

Relapse at 7–12 months

- Drug 27%
- Placebo 64%

Effect sizes of general medicine and psychiatric drugs



- Review of
 - 94 meta-analyses of 48 general medicine drugs
 - 33 meta-analyses of 16 psychiatric drugs

Negative symptoms of schizophrenia

Primary negative symptoms

- Direct causality
- Primary manifestation of schizophrenia
- Enduring symptoms

Secondary negative symptoms

- Consequence of EPS
- Depressive symptoms
- Disorganised or paranoid withdrawal

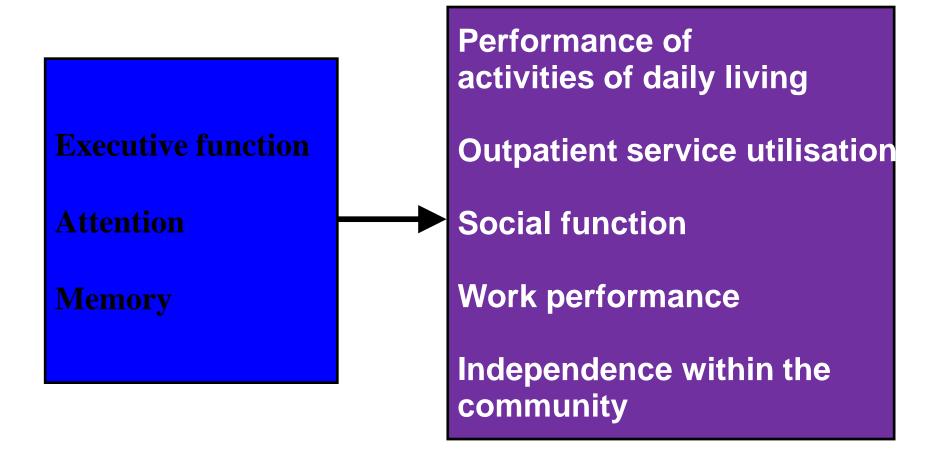
D2 blockade impairs negative symptoms

Arango et al 2004, Artaloyta et al 2008

Antipsychotics and negative symptoms

- SGA do not seem to improve primary enduring negative symptoms (Arango et al 2004)
- Some FGA and SGA cause negative symptoms in healthy controls (Artaloytia, Arango et al 2006)
- Patients with negative symptoms are at higher risk to develop Metabolic Syndrome (Arango et al 2008)

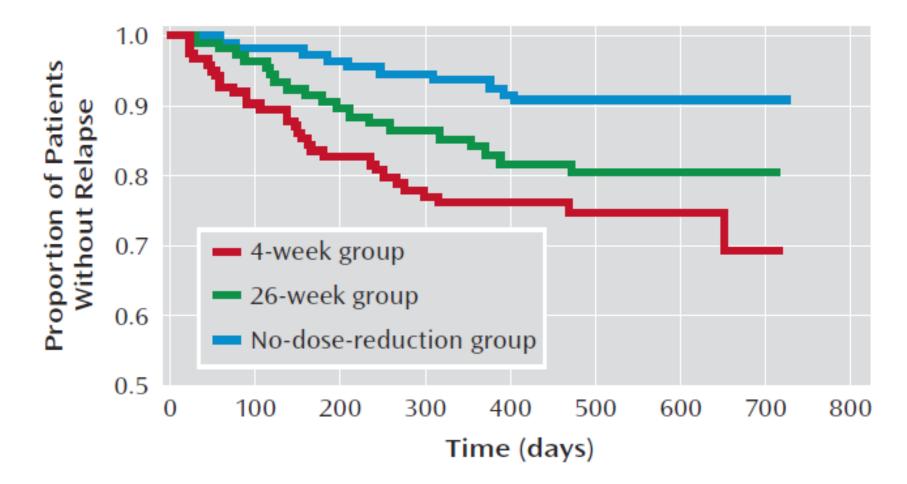
Cognitive deficits predict functional outcomes



D2 blockade impairs cognition

Velligan et al 1997; Green et al 2000; Bryson & Bell 2003; McGurk et al 2004

50% dose reduction after four weeks or 26 weeks was associated with significantly more relapses than keeping the initial dose



Starting dose: risperidone 4-8mg/day

Wang et al. AJP 2010

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Haloperidol Dosing

- With acute treatment, check for cogwheel rigidity daily as haloperidol, started at 1-2 mg per day, is increased by 1-2 mg every other day.
- For antipsychotic porpoises no need to go above 6-8 mg/day. Maintenance: 2-4 mg/day
- Oral, acute IM, depot

Risperidone Dosing

- 3-6 mg per day for 3-6 weeks as an antipsychotic
- A dose that produces parkinsonian side effects is probably too high a dose
- First exposure: 0.5 mg bid, then 1 mg bid
- Acute exacerbation: 1 mg bid, then 2 mg bid
- Elderly: 50% of above, or less
- P450 Drug Interactions: 2D6 substrate

Olanzapine Dosing

- Works most quickly when *started* at 10-20 mg/d*
- Smoking increases clearance by 40%** (58-88% of patients with schizophrenia smoke)
- Female gender decreases clearance by 30%**
- Should you exceed the PDR max. dose of 20 mg? (the *average* dose used in CATIE) Not routinely.

* Osser (2001)

**Package Insert, Weiss (2005), Carrillo (2003)

Metabolic Issues w. Olanzapine

- More than 50% of olanzapine patients gain > 7% body wgt (naïve: 75%)
- Elevated triglycerides highest with olanzapine
- HgbA1C increased the most with olanzapine
- Triglycerides v. strongly correlated with insulin resistance (IR)

Ziprasidone

- Half-life 10 hours
- Avoid ziprasidone if EKG shows QTc is >500 milliseconds
- On medications that might prolong the QTc since this EKG was done? (tricyclics, quetiapine, thioridazine, floxacins.) If so, repeat EKG
- Risk for electrolyte problems? (alc. Dependent, purging bulimic) If so, get K+, Mg++ and follow

Dosing of Ziprasidone - 1

- Package insert recommends starting at 20 mg twice daily, but 3/4 acute treatment studies in patients with schizophrenia failed to show superiority of 20 mg bid to placebo
- Stable outpatient being switched: could start with 40 mg bid. Continuation with the other drug is recommended (at least 1 week)
- Absorption is reduced by 40% if not taken with food

Dosing of Ziprasidone - 2

- Raise the dose, as tolerated, every 1-2 days to 80 bid for the routine case of an acutely ill hospitalized patient with schizophrenia
- If this is a first episode patient, try perhaps half the routine dose
- Major clinical concern: difficult to find the right dose!

Aripiprazole Issues

- 75 hour half life
- Substrate for Cytochrome P450 3A4 and 2D6. Paroxetine and fluoxetine will raise levels (use 50% dose), carbamazepine will lower them.
- 15 mg is superior to 30 mg, at all data points and even after 1 week
- 30 mg sometimes needed in clinical practice in mania and acute schizophrenia

Kane et al 2002, Pigott 2003

Aripiprazole Side Effects

- Dizziness
- Insomnia (prescribe in the morning)
- Akathisia, agitation
- Headache
- Sedation

Quetiapine

- Half-life 6-12 hours
- Starting dose 100-200 mg/day. Rapid titration if needed
- Bipolar depression: 300 mg/day
- Acute schizophrenia: up to 1200 mg/day
- Bipolar mania: 600-800 mg/day
- Maintenance: 300-500 mg/day
- Widely used outside schizophrenia

Smith et al 2005

Amisulpride

- Half-life 12 hours
- Low dose: 50-200 mg/day. Block inhibitory pre-synaptic autoreceptors: facilitation of dopamine (negative symptoms)
- Dose: 400-1200 mg/day. Block D2 (partial agnonist)-D3 receptors (5HT₇ antagonist)
- Activate the GHB receptor (inhibit DA release)

Paliperidone

- 9-OH- Risperidone
- Half life 23 hours
- Not metabolized by Cytochrome P450 (Patients with hepatic compromise)
- Dose between 6-12 mg/day

Asenapine

• In Europe approved only for bipolar disorder

• Sublingual

• Half-life 20 hours

• Starting dose: 10 mg bid (5 mg bid if adjunct to lithium or valproate or schizophrenia)

Sertindole

• Reintroduced in 2002 for restricted use

• Half life 72 hours

• Initiate 4 mg/day. Increase 4 mg/day

• Maximum dose 20 mg

• Extensive ECG monitoring requierement

Lurasidone

- 18.5, 37 and 74 mg
- Starting dose: 37 mg/day once a day
- Akathisia and somnolence

Clozapine Dosing

- 12.5 mg for first dose. Thereafter, divided doses
- Increase by 25-50 mg per day as tolerated, to 300-400 mg per day. Maximum is 900 mg/d
- If response unsatisfactory, check **plasma level**. Best results are with levels of parent compound greater than 400 ng/ml

No single dose should exceed 450 mg

CBC Monitoring with Clozapine

- Changes from country to country. Weekly CBC for 16 weeks. Then every 4 weeks
- If WBC < 3.5 or ANC 1.5-2.0, repeat CBC and get biweekly CBC until levels rise.
- If WBC < 3.0 or ANC 1.0-1.5, hold clozapine, get daily CBC until levels rise. Rechallenge possible
- If WBC <2.0 or ANC <1.0, stop clozapine. Monitor daily. Rechallenge not advised, though there are some reports.

Clozapine

- Approved for suicide within schizophrenia
- Only antipsychotic with partial evidence for polydipsia and nicotine addiction

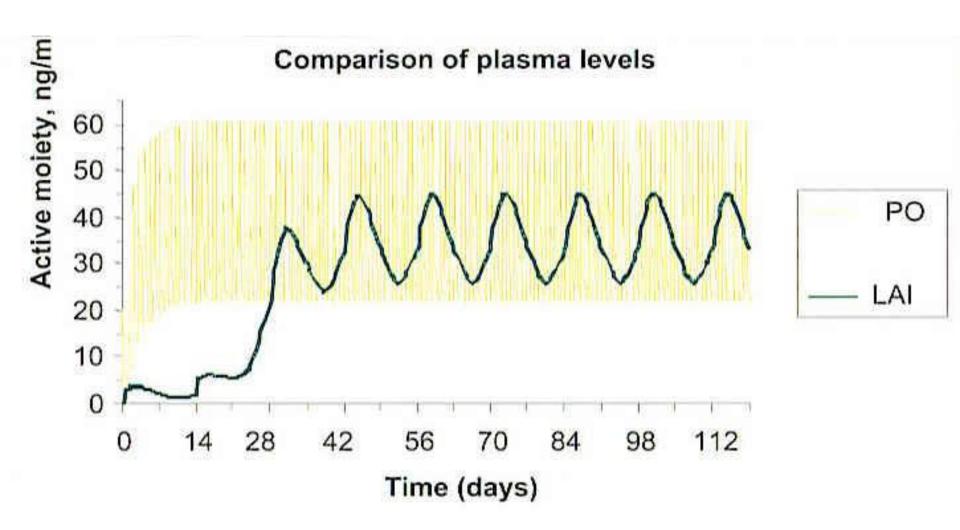
Other antipsychotics approved in the US or in their way

- Iloperidone
- Brexpiprazole

Depot (LAI) Neuroleptics

- Fluphenazine Decanoate: 12.5 mg to 50 mg every two weeks.
- Haloperidol Decanoate 25 mg to 200 mg every 4 weeks.
- Risperidone consta every 2 weeks (12.5 mg, 25 mg, 37.5 mg, 50mg)
- Olanzapine depot (2-4 weeks, post-injection syndrome, at least 3hour monitoring)

• Many more patients are non-compliant or not



Mannaert E et al. Poster 530. CINP. Paris, June 20-24, 2004

Paliperidone Palmitate

• Paliperidone Palmitate: (50mg, 75 mg, 100 mg) Mean doses 73.3 and 104.6 mg every four weeks

 Paliperidone palmitate (Trivecta): maintenance treatment of schizophrenia in adult patients who are clinically stable on Xeplion® (234 mg, 156 mg, 117 mg, 78 mg)

Aripiprazole LAI

• 300/400 mg IM once a month

ORIGINAL ARTICLE

Long-Acting Risperidone and Oral Antipsychotics in Unstable Schizophrenia

Robert A. Rosenheck, M.D., John H. Krystal, M.D., Robert Lew, Ph.D., Paul G. Barnett, Ph.D., Louis Fiore, M.D., M.P.H., Danielle Valley, M.P.H., Soe Soe Thwin, Ph.D., Julia E. Vertrees, Pharm.D., and Matthew H. Liang, M.D., M.P.H., for the CSP555 Research Group* N Engl J Med 2011;364:842-51. Copyright © 2011 Massachusetts Medical Society.

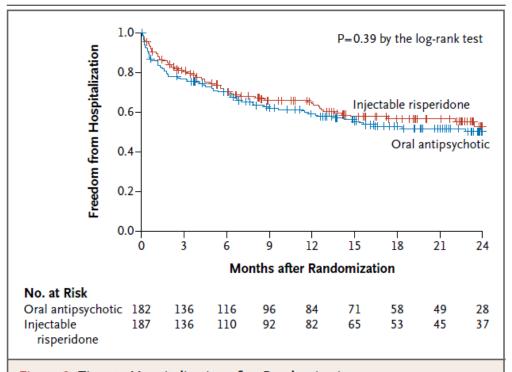


Figure 2. Time to Hospitalization after Randomization.

In this analysis, data on patients who withdrew from the study were censored at the time of withdrawal from the study.

Most recent meta-analysis...

	LAI		OAP			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total I		Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.7.1 Relapse (estimat							
Barnes 1983	3	19	., ionge.	17	1.0%	0.89 [0.21, 3.85]	
Crawdford 1974	2	14	6	15	1.0%	0.36 [0.09, 1.48]	
Del Guidice 1975	21	27	59	61	9.5%	0.80 [0.65, 0.99]	
Falloon 1978	21	20	5	24	9.5% 2.1%	1.92 [0.74, 4.95]	
Hogarty 1979	22	20 55	36	24 50	6.8%	0.56 [0.38, 0.80]	
Kaneno 1991	8	127	9	132	2.2%	0.92 [0.37, 2.32]	
Rifkin 1977	2		3		0.7%		
		23		28		0.81 [0.15, 4.45]	_
Schooler 1980 Subtotal (95% CI)	54	107 392	61	107 434	8.8% 32.1%	0.89 [0.69, 1.14] 0.79 [0.65, 0.96]	•
Total events	120		182				
Heterogeneity: Tau ² = 0				= 0.25); I ² = 23%		
Test for overall effect: 2	2 = 2.33 (F	P = 0.02)					
1.7.2 Relapse (estimat	ted rate p	referred	l, longes	st time	point) - Ha	loperidol depot	
Glick 2005	5	9	9	16	3.1%	0.99 [0.48, 2.04]	<u> </u>
Subtotal (95% CI)		9		16	3.1%	0.99 [0.48, 2.04]	-
Total events	5		9				
Heterogeneity: Not app Test for overall effect: Z		P = 0.97)					
1.7.3 Relapse (estimat	ted rate p	referred	l, longes	st time	point) - Ol	anzapine LAI	
Detke 2011	102	264	104	260	9.4%	0.97 [0.78, 1.19]	+
Kane 2010	58	599	23	322	5.5%	1.36 [0.85, 2.16]	+
\ane ∠010	58						
	58	863		582	14.9%	1.08 [0.78, 1.47]	—
Subtotal (95% CI)	160		127	582	14.9%	1.08 [0.78, 1.47]	-
Subtotal (95% CI) Total events	160	863				1.08 [0.78, 1.47]	•
Kane 2010 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0 Test for overall effect: 2	160 0.03; Chi²	863 = 1.77, d	df = 1 (P			1.08 [0.78, 1.47]	•
Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0 Test for overall effect: 2	160 0.03; Chi² Z = 0.45 (P	863 = 1.77, c ? = 0.65)	df = 1 (P	= 0.18); I ² = 44%		Ť
Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0 Test for overall effect: 2 1.7.4 Relapse (estimat	160 0.03; Chi ² : Z = 0.45 (P ted rate p	863 = 1.77, c ? = 0.65) referred	df = 1 (P	= 0.18 st time); l² = 44% point) - Ris	speridone LAI	—
Subtotal (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 1.7.4 Relapse (estimat Bai 2007	160 0.03; Chi² 2 = 0.45 (P ted rate p 2	863 = 1.77, c ? = 0.65) referred 23	df = 1 (P I, longe: 0	= 0.18 st time 25); l ² = 44% point) - Ris 0.2%	speridone LAI 5.42 [0.27, 107.20]	
Subtotal (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 T.7.4 Relapse (estimat Bai 2007 Gaebel 2010	160 0.03; Chi ² 2 = 0.45 (P ted rate p 2 65	863 = 1.77, c ? = 0.65) referred 23 327	df = 1 (P I, longes 0 122	= 0.18 st time 25 326); l ² = 44% point) - Ri 0.2% 8.6%	speridone LAI 5.42 [0.27, 107.20] 0.53 [0.41, 0.69]	
Subtotal (95% Cl) Total events Heterogeneity: Tau ² = 0 Test for overall effect: 2 1.7.4 Relapse (estimat Bai 2007 Gaebel 2010 Kamijima 2009	160 0.03; Chi ² Z = 0.45 (F ted rate p 2 65 18	863 = 1.77, c ? = 0.65) referred 23 327 147	df = 1 (P I, longe: 0 122 5	= 0.18 st time 25 326 51); l ² = 44% point) - Ri 0.2% 8.6% 2.1%	speridone LAI 5.42 [0.27, 107.20] 0.53 [0.41, 0.69] 1.25 [0.49, 3.19]	
Subtotal (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 1.7.4 Relapse (estimat Bai 2007 Gaebel 2010 Kamijima 2009 Keks 2007	160 0.03; Chi ² ; Z = 0.45 (P ted rate p 2 65 18 25	863 = 1.77, c ? = 0.65) referred 23 327 147 247	df = 1 (P I, longes 0 122 5 27	= 0.18 st time 25 326 51 300); l ² = 44% point) - Ri : 0.2% 8.6% 2.1% 4.9%	5.42 [0.27, 107.20] 0.53 [0.41, 0.69] 1.25 [0.49, 3.19] 1.12 [0.67, 1.89]	
Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.7.4 Relapse (estimat Bai 2007 Gaebel 2010 Kamijima 2009 Keks 2007 MacFadden 2010	160 $2.03; Chi^2 + 100$ $2 = 0.45 (F)^2$ ted rate p 2 65 18 25 90	863 = 1.77, c ? = 0.65) referred 23 327 147 247 177	df = 1 (P I, longes 0 122 5 27 82	= 0.18 St time 25 326 51 300 172); l ² = 44% point) - Ris 0.2% 8.6% 2.1% 4.9% 9.4%	5.42 [0.27, 107.20] 0.53 [0.41, 0.69] 1.25 [0.49, 3.19] 1.12 [0.67, 1.89] 1.07 [0.86, 1.32]	
Subtotal (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 1.7.4 Relapse (estimat Bai 2007 Gaebel 2010 Kamijima 2009 Keks 2007 MacFadden 2010 NCT00246259	160 0.03; Chi ² - Z = 0.45 (F ted rate p 2 65 18 25 90 11	863 = 1.77, c = 0.65) referred 23 327 147 247 177 32	df = 1 (P I, longes 0 122 5 27 82 5	= 0.18 st time 25 326 51 300 172 31); ² = 44% point) - Ris 0.2% 8.6% 2.1% 4.9% 9.4% 2.1%	5.42 [0.27, 107.20] 0.53 [0.41, 0.69] 1.25 [0.49, 3.19] 1.12 [0.67, 1.89] 1.07 [0.86, 1.32] 2.13 [0.84, 5.43]	
Subtotal (95% CI) Total events Heterogeneity: Tau² = (Test for overall effect: 2 1.7.4 Relapse (estimat Bai 2007 Gaebel 2010 Keks 2007 Keks 2007 MacFadden 2010 NCT00246259 Potapov 2008	160 .03; Chi ² - Z = 0.45 (F ted rate p 2 65 18 25 90 11 4	863 = 1.77, c = 0.65) referred 23 327 147 247 177 32 20	df = 1 (P I, longes 0 122 5 27 82 5 8	= 0.18 st time 25 326 51 300 172 31 20); ² = 44% point) - Ri : 0.2% 8.6% 2.1% 4.9% 9.4% 2.1% 1.8%	5.42 [0.27, 107.20] 0.53 [0.41, 0.69] 1.25 [0.49, 3.19] 1.12 [0.67, 1.89] 1.07 [0.86, 1.32] 2.13 [0.84, 5.43] 0.50 [0.18, 1.40]	
Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0 Fest for overall effect: 2 1.7.4 Relapse (estimat Bai 2007 Gaebel 2010 Kamijima 2009 Keks 2007 MacFadden 2010 NCT00246259 Potapov 2008 Rosenheck 2011	160 .03; Chi ² - Z = 0.45 (F ted rate p 2 65 18 25 90 11 4 86	863 = 1.77, c > = 0.65) referred 23 327 147 247 177 32 20 187	df = 1 (P I, longes 0 122 5 27 82 5 8 90	= 0.18 st time 25 326 51 300 172 31 20 182); ² = 44% point) - Ri : 0.2% 8.6% 2.1% 4.9% 9.4% 1.8% 9.4%	5.42 [0.27, 107.20] 0.53 [0.41, 0.69] 1.25 [0.49, 3.19] 1.12 [0.67, 1.89] 1.07 [0.86, 1.32] 2.13 [0.84, 5.43] 0.50 [0.18, 1.40] 0.93 [0.75, 1.15]	
Subtotal (95% CI) Total events Heterogeneity: Tau² = (Test for overall effect: 2 1.7.4 Relapse (estimat Bai 2007 Gaebel 2010 Kamijima 2009 Keks 2007 MacFadden 2010 NCT00246259 Potapov 2008 Rosenheck 2011 Schooler 2011	160 0.03; Chi ² Z = 0.45 (F ted rate p 2 65 18 25 90 11 4 86 75	863 = 1.77, c > = 0.65) referred 23 327 147 247 177 32 20 187 146	df = 1 (P I, longes 0 122 5 27 82 5 8	= 0.18 st time 25 326 51 300 172 31 20 182 150); ² = 44% point) - Ris 0.2% 8.6% 2.1% 9.4% 2.1% 1.8% 9.4% 8.8%	5.42 [0.27, 107.20] 0.53 [0.41, 0.69] 1.25 [0.49, 3.19] 1.12 [0.67, 1.89] 1.07 [0.86, 1.32] 2.13 [0.84, 5.43] 0.50 [0.18, 1.40] 0.93 [0.75, 1.15] 1.24 [0.97, 1.59]	
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Subtotal (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 1.7.4 Relapse (estimat Bai 2007 Gaebel 2010 Kamijima 2009 Keks 2007 MacFadden 2010 NCT00246259 Potapov 2008 Rosenheck 2011 Schooler 2011 Subtotal (95% CI) Total events	160 0.03; Chi ² ; Z = 0.45 (F ted rate p 2 65 18 25 90 11 4 86 75 376	863 = 1.77, c > = 0.65) referred 23 327 147 247 177 32 20 187 146 1306	I, longes 0 122 5 27 82 5 8 90 62 401	= 0.18 st time 25 326 51 300 172 31 20 182 150 1257); I ² = 44% point) - Ris 0.2% 8.6% 2.1% 4.9% 9.4% 2.1% 1.8% 9.4% 8.8% 47.4%	5.42 [0.27, 107.20] 0.53 [0.41, 0.69] 1.25 [0.49, 3.19] 1.12 [0.67, 1.89] 1.07 [0.86, 1.32] 2.13 [0.84, 5.43] 0.50 [0.18, 1.40] 0.93 [0.75, 1.15] 1.24 [0.97, 1.59] 0.98 [0.74, 1.28]	
Subtotal (95% CI) Total events Heterogeneity: Tau² = (Test for overall effect: 2 1.7.4 Relapse (estimat Bai 2007 Gaebel 2010 Keks 2007 MacFadden 2010 NCT00246259 Potapov 2008 Rosenheck 2011 Subtotal (95% CI) Total events Heterogeneity: Tau² = (160 0.03; Chi ² : Z = 0.45 (F ted rate p 2 65 18 25 90 11 4 86 75 376 0.10; Chi ² :	863 = 1.77, c > = 0.65) referred 23 327 147 247 177 32 20 187 146 1306 = 31.71,	df = 1 (P 1, longes 0 122 5 27 82 5 8 90 62 401 df = 8 (I	= 0.18 st time 25 326 51 300 172 31 20 182 150 1257); I ² = 44% point) - Ris 0.2% 8.6% 2.1% 4.9% 9.4% 2.1% 1.8% 9.4% 8.8% 47.4%	5.42 [0.27, 107.20] 0.53 [0.41, 0.69] 1.25 [0.49, 3.19] 1.12 [0.67, 1.89] 1.07 [0.86, 1.32] 2.13 [0.84, 5.43] 0.50 [0.18, 1.40] 0.93 [0.75, 1.15] 1.24 [0.97, 1.59] 0.98 [0.74, 1.28]	
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LAI, long-acting injectable; OAP, oral antipsychotic; M-H, Mantel–Haenszel; Random, random effects model; CI, confidence interval

A Nationwide Cohort Study of Oral and Depot Antipsychotics After First Hospitalization for Schizophrenia

TABLE 1. Pairwise Comparisons for Risk of All-Cause Discontinuation of the Initial Antipsychotic Treatment and Risk of Rehospitalization After a First Hospitalization for Schizophrenia^a

	All-Cause	Discontinua	tion	Rehospitalization		
Comparison	Adjusted Hazard Ratio ^b	95% CI	р	Adjusted Hazard Ratio⁵	95% CI	р
Any depot injection compared with equivalent oral formulation	<mark>0.41</mark>	0.27–0.61	<0.0001	0.36	0.17–0.75	0.007
Haloperidol depot injection compared with oral haloperidol	0.27	0.08–0.88	0.03	0.12	0.01–1.13	0.06
Perphenazine depot injection compared with oral perphenazine	0.32	0.19-0.53	<0.0001	0.53	0.22-1.28	0.16
Risperidone depot injection compared with oral risperidone	0.44	0.31–0.62	<0.0001	0.57	0.30-1.08	0.09
Zuclopenthixol depot injection compared with oral zuclopenthixol	0.75	0.29–1.89	0.54	0.49	0.11-2.14	0.35

Jari Tiihonen, M.D., Ph.D. (Am J Psychiatry 2011; 168:603–609)

Outline of Lecture

- Introduction
- Algorithm for selecting antipsychotics.
- What do they treat and what they do not treat
- Most common antipsychotics: minimal facts we should know about them
- Efficacy
- Safety and tolerability

Why Olanzapine Beats Risperidone, Risperidone Beats Quetiapine, and Quetiapine Beats Olanzapine: An Exploratory Analysis of Head-to-Head Comparison Studies of Second-Generation Antipsychotics

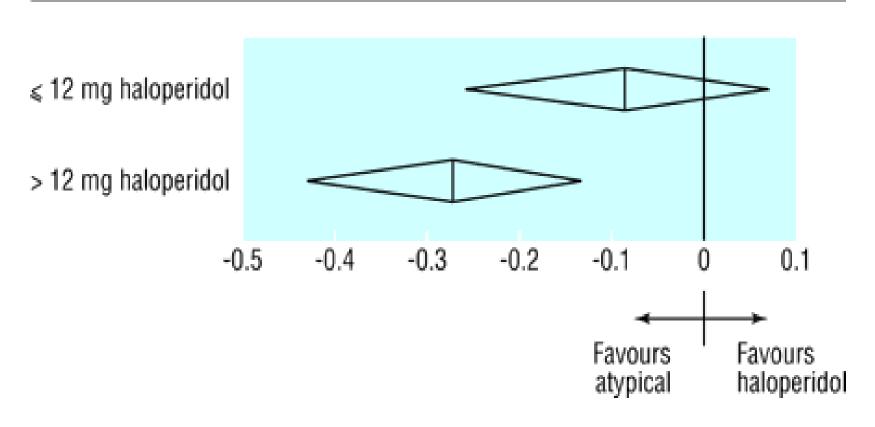
The overall outcome reported in the abstract of head to head comparisons of atypical antipsychotics strongly depends on **the sponsor**

In a blinded analysis of the abstracts of 33 head to head comparisons of atypical antipsychotics in about 90% the overall outcome was in favour of the sponsor

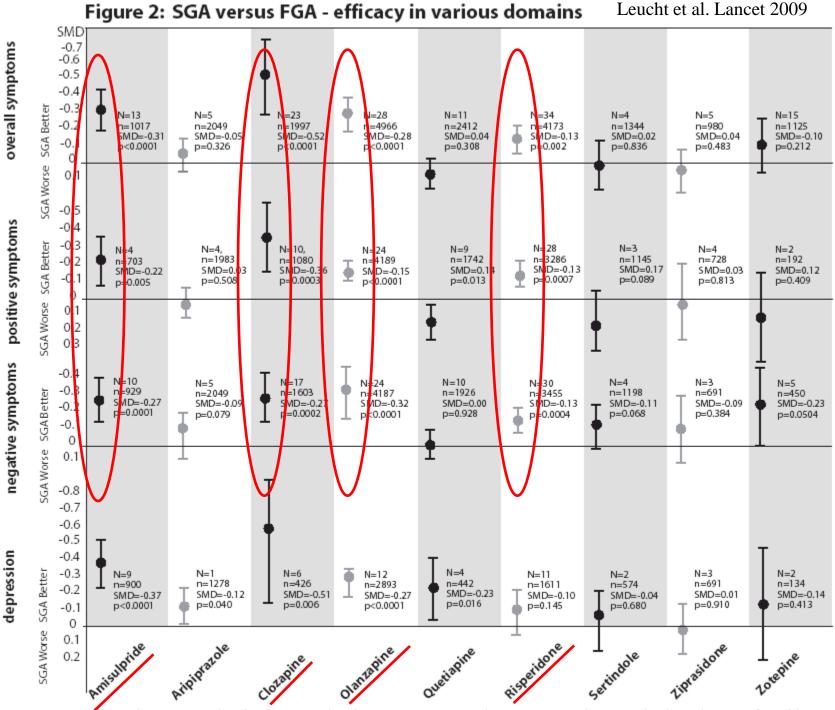
Heres et al. Am J Psych 2006

Meta-analysis of atypical antipsychotics in the treatment of schizophrenia

Geddes et al 2000



Overall symptom score by dose of comparator drug



and a set of the set o

NNT

- Schizophrenia: 5-10
- Bipolar mania: 3-6
- Aggression in autism: 3-4

Outline of Lecture

- Introduction
- Algorithm for selecting antipsychotics.
- What do they treat and what they do not treat
- Most common antipsychotics: minimal facts we should know about them
- Efficacy
- Safety and tolerability

SEDATION Greater with CLOZAPINE, OLANZAPINE, QUETIAPINE HEADACHE

SUBJECTIVE BURDEN

- Loss of energy/drive Greater with classic
- I Dysphoria Greater with classic
- Problems with memory and concentration

SLEEP DISTURBANCE

- Night sleep pattern
- Difficulty waking/daytime sleepiness
- Insomnia Greater with ARIPIPRAZOLE

CARDIOVASCULAR

- | Palpitations/tachycardia ? Greater with QUETIAPINE
- | Postural hypotension Greater with CLOZAPINE, LEVOMEPROMAZINE
- ECG abnormalities
- | QT prolongation Greater with SERTINDOLE, ZIPRASIDONE GASTROINTESTINAL
 - I Nausea/vomiting, constipation, diarrhoea

ENDOCRINE

- Weight gain Greater with CLOZAPINE and OLANZAPINE
- I Diabetes Greater with CLOZAPINE and OLANZAPINE
- I Decreased T3 Greater with QUETIAPINE

HEPATIC DYSFUNCTION

- I Increased transaminases ? Greater with OLANZAPINE
- I Cholestatic jaundice

HYPERSALIVATION Greater with CLOZAPINE ANTICHOLINERGIC EFFECTS

I Dry mouth / Blurred vision / Urinary hesitancy NOCTURNAL ENURESIS Greater with RISPERIDONE SEXUAL SIDE-EFFECTS Greater with RISPERIDONE, AMISULPRIDE

- Loss of libido
- Females: Anorgasmia/Change in menstruation
- Males: Erectile dysfunction/Ejaculatory disturbance

? Reduced ejaculatory volume with SERTINDOLE

PROLACTIN ELEVATION Dose-related with RISPERIDONE, AMISULPRIDE

CNS

- Emergence of disorientation/clouding of consciousness
- Seizures Greater with CLOZAPINE,? Classic antipsychotics

Neuroleptic malignant syndrome Classic OPHTHALMOLOGICAL

- I Glaucoma
- Corneo-lenticular opacities/pigmentary lesions
 CUTANEOUS REACTIONS
 - I Photosensitive skin rash
 - I Pigmentation

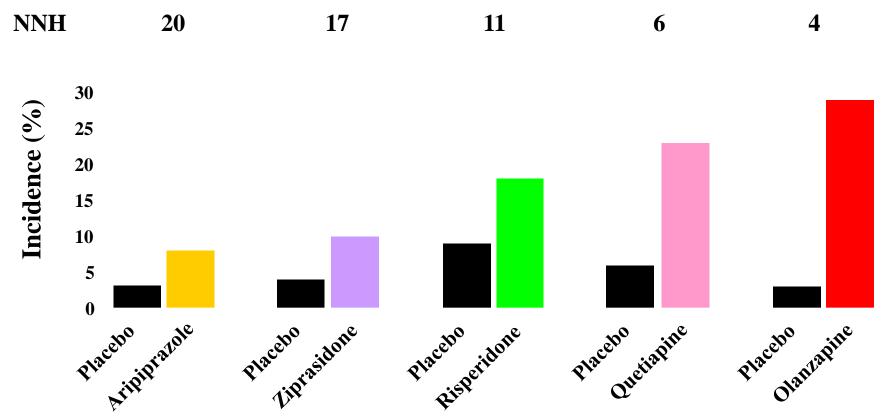
HAEMATOLOGICAL

Blood dyscrasias Greater with CLOZAPINE

ANTIPSYCHOTIC-INDUCED **MOVEMENT DISORDER** Early onset Parkinsonism (Classic potent D2) Acute akathisia (Classic, aripiprazole) Acute dystonia (Classic potent D2, risperidone dose dependant) Late onset Chronic akathisia ? Tardive dystonia ? Tardivo dvekinocia (classia)

Clinically Significant Weight Gain (≥7%)

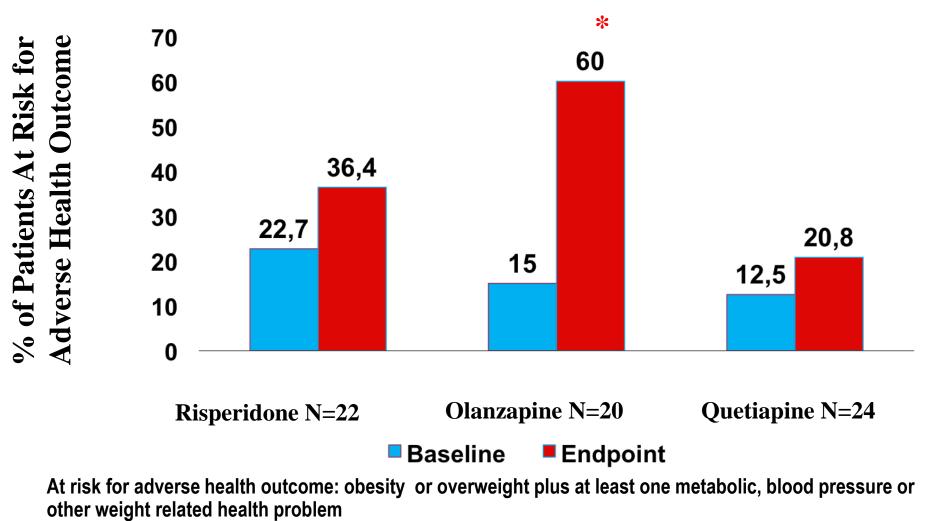




NNH = number needed to harm

Abilify[®] (aripiprazole) US PI, October 2006. Geodon[®] (ziprazidone) US PI, August 2004. Risperdal[®] (risperidone) US PI, November 2006. Seroquel[®] (quetiapine fumarate) US PI, July 2007. Zyprexa[®] (olanzapine) US PI, March 2002.

Change in At Risk Health Status During 6-Month Naturalistic Antipsychotic Treatment

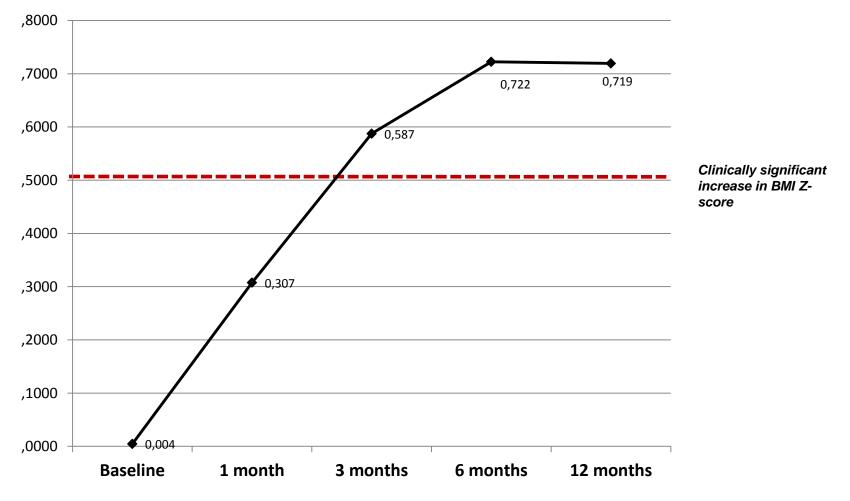


* p <.05; group comparison: p=.018

Fraguas D et al. (2008), J Clin Psychiatry ;69(7):1166-75.

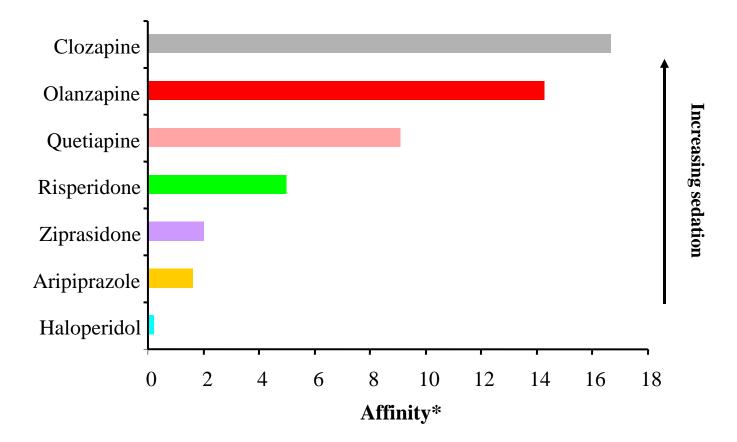
One-year longitudinal study of children and adolescents treated with SGAs

Change in BMI z-score



Diaz-Caneja, Penzol et al. In preparation

Sedation may be Related to Affinity of Medications for the Histamine H1 Receptor



*Presented at $10^2 \times 1/\text{Ki}$ (nM) **Data with cloned human receptors

Bymaster FP et al. Neuropsychopharmacology 1996;14:87-96;

Post-Lecture Exam Question 1

- 1. Which of the following is an antipsychotic dose that is in excess of the optimal?
 - A. Aripiprazole 15 mg/day
 - B. Ziprasidone 80 mg bid
 - C. Haloperidol 20 mg qd
 - D. Risperidone 4 mg/day
 - E. Quetiapine 300 mg bid

- 2. Which of the following antipsychotics must be taken with food in order to prevent significant loss of absorption?
 - A. Ziprasidone
 - B. Olanzapine
 - C. Clozapine
 - D. Aripiprazole
 - E. Risperidone

- 3. Which of the following is the recommended starting dose for clozapine?
 - A. 25 mg twice a day
 - B. 12.5 mg
 - C. 25 mg
 - D. 50 mg

- 4. All of the following are true of a patient on risperidone who gets parkinsonian side effects, except:
 - A. D2 receptor occupancy is 75% or more
 - B. The patient is above the "neuroleptic threshold"
 - C. Patient is at risk for secondary negative symptoms
 - D. Raising the dose is likely to be helpful

- 5. ¿What is the drug of choice for a schizophrenia patient with polydispia?
 - A. Olanzapine
 - B. Thirodazine
 - C. Ziprasidone
 - D. Pimozide
 - E. Clozapine

The NNT for antipsychotics is lower for

- A. Schizophrenia
- B. Schizoaffective disorder
- C. Bipolar disorder
- D. Aggressive behaviour in autism
- E. Depression

Which one of these antipsychotics has a longer half life

- A. Olanzapine
- B. Haloperidol
- C. Chrlopromazine
- D. Aripiprazole
- E. Quetiapine

Which one of these antipsychotics is the only one that does not have affinity for the D2 receptor

- A. Paliperidone
- B. Quetiapine
- C. Chrlopromazine
- D. Aripiprazole
- E. None

- When do we have plasma levels similar to oral risperidone with Risperidone consta (25 mg)
 - A. Day 1
 - B. Day 5
 - C. Day 10
 - D. Day 15
 - E. Day 30

What antipsychotic would you not recommend for a 16 year old with a first psychotic episode

- A. Aripiprazole
- B. Risperidone
- C. Quetiapine
- D. Olanzapine
- E. Haloperidol (low dose)

- For what drug do guidelines (e.g PORT) recommend to measure plasma levels (therapeutic window)?
 - A. Aripiprazole
 - B. Clozapine
 - C. Quetiapine
 - D. Olanzapine
 - E. Haloperidol

- Most of the weight gain with antipsychotics takes place in:
 - A. First month
 - B. 3 months
 - C. 6 months
 - D. 1 year
 - E. 2 years

The half life of LAI (depot) antipsychotics is:

- A. 2 weeks
- B. 4 weeks
- C. 12 weeks
- D. A and B are correct
- E. A, B and C are correct