

# NOUS REPTES EN L'ELECCIÓ D'UN PSICOFÀRMAC

## Aspectes clínics, afavorint l'adherència

A. MANÉ



Estudi i Tractament  
d'Episodis Psicòtics

**INAD**  
Institut de  
Neuropsiquiatria  
i Addiccions

Parc  
de Salut  
**MAR**  
Barcelona



# INDEX

- Evolució del tractament antipsicòtic oral i eficàcia
- Recaigudes a l'esquizofrènia
  - Risc
  - Conseqüències
  - Factors de risc (adherència, insight, tòxics)
- Estratègies d'actuació per evitar recaigudes:
  - Entrevista motivacional
  - Psicoeducació
  - Antipsicòtics llarga durada
- Conclusions

# Evolució tractaments antipsicòtics (orals)

50s

60s

70s

90s

00

10

↑  
Clorpromazina

↑  
Haloperidol  
Flufenazina  
Perfenazina  
Loxapina

↑  
Clozapina

↑  
Risperidona  
Olanzapina  
Quetiapina  
Ziprasidona

↑  
Aripiprazol  
Paliperidona

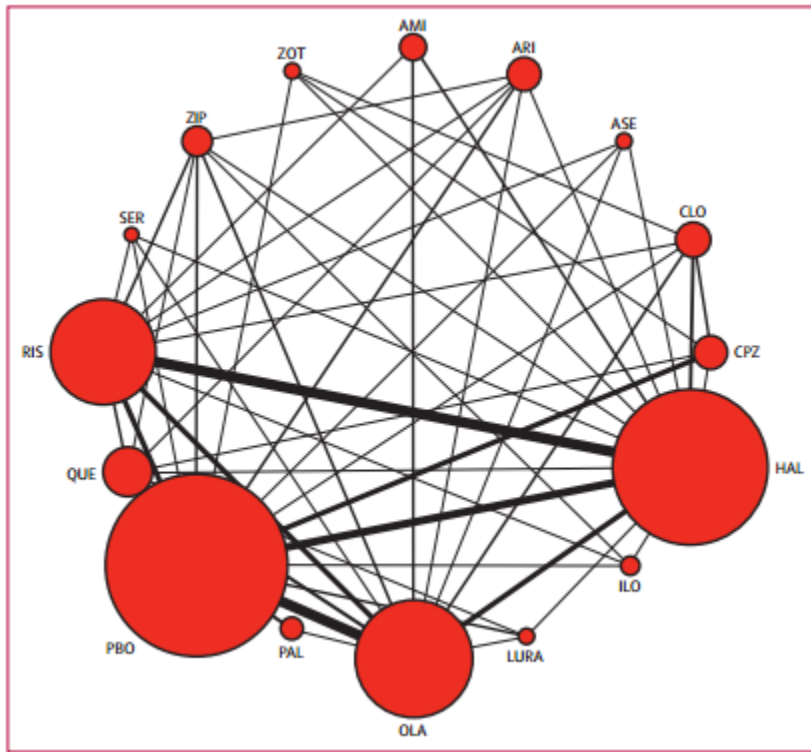
↑  
Asenapina

**TÍPICS**

**ATÍPICS**

# 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



Petites diferències en eficàcia però possiblement clínicament rellevants

Diferent perfil d'efectes secundaris

La decisió terapèutica s'hauria de basar en avaluació dels diferents dominis:

- Eficàcia
- Discontinuació
- Augment de pes
- Increment de prolactina
- S. Extrapiramidals
- Augment del QTc
- Sedació

# PREVALENÇA RECAIGUDES ESQUIZOFRENIA

N=104				
*Años desde el primer episodio psicótico.				
*Años	Recaídas	Intervalo 95%.		Pacientes en riesgo al final del año
		Superior	Inferior	
1	16.2	8.9	23.4	80
2	53.7	43.4	64.0	39
3	63.1	52.7	73.4	22
4	74.7	64.2	85.2	9
5	<b>81.9</b>	70.6	93.2	4

Robinson, D. et al. Arch. Gen. Psychiatr., 1999. 56: 241-247.

# CONSEQÜÈNCIES DE LA RECAIGUDA

- Conseqüències del propi episodi (personal, familiar, situacions de risc)
- Impacte en la recuperació funcional (acadèmica, social)
- Major resistència al tractament
- Impacte econòmic (major en psicosis no estable)
- S'han associat a alteracions cerebrals

*1- Emsley et al Sch Research 2013; 2. Almond et al. Br J Psychiatry 2004.*

# Natural Course of Schizophrenic Disorders: A 15-Year Followup of a Dutch Incidence Cohort

by Durk Wiersma, Fokko J. Nienhuis, Cees J. Slooff, and Robert Giel

*Schizophrenia Bulletin*, Vol. 24, No. 1, 1998

- 1/6 no remet després d'un episodi, independentment quin episodi es tracta
- 1/5 remet parcialment, amb persistència símptomes negatius



Cronicitat augmenta de  $\frac{1}{4}$  després 1r episodi a  $\frac{1}{2}$  després del quart

- Augment progressiu de la durada de l'episodi (9 a 27 mesos)

# CONSEQÜÈNCIES DE LA RECAIGUDA

- Conseqüències del propi episodi (personal, familiar, situacions de risc)
- Impacte en la recuperació funcional (acadèmica, social)
- Contribució en l'estigma
- Major resistència al tractament
- Impacte econòmic (major en psicosis no estable)
- S'han associat a alteracions cerebrals

*1- Emsley et al Sch Research 2013; 2. Almond et al. Br J Psychiatry 2004.*



BRITISH JOURNAL OF PSYCHIATRY (2004), 184, 346-351

## **Relapse in schizophrenia: costs, clinical outcomes and quality of life**

STEPHEN ALMOND, MARTIN KNAPP, CLEMENT FRANCOIS,  
MONDHER TOUMI and TRAOLACH BRUGHA

**Table 5** Mean 6-month service use and costs (£, 1998) per patient by relapse status

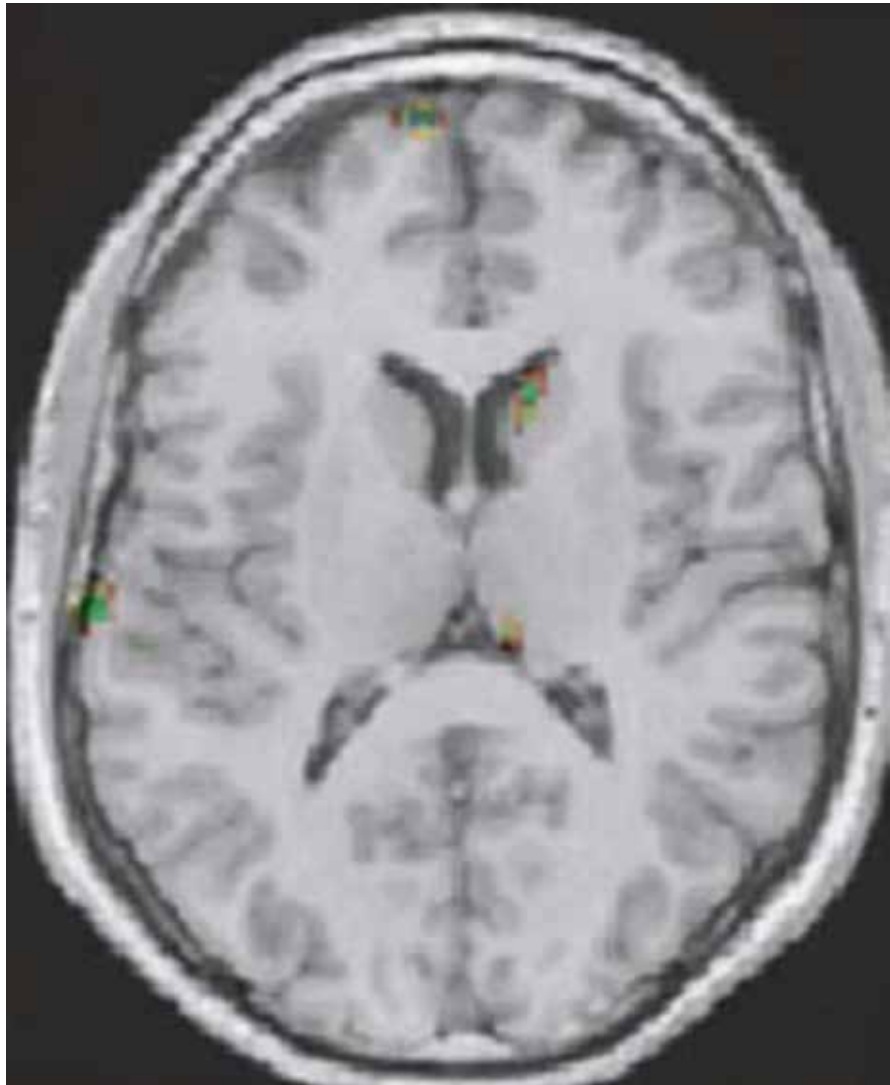
Service	Non-relapse (n=68)		Relapse (n=77)	
	Mean usage	Costs (£)	Mean usage	Costs (£)
In-patient care (days) <sup>1</sup>	0.0	0	57.8	6451
Out-patient				
Psychiatric visits <sup>1</sup>	1.4	135	2.1	209
Other <sup>2</sup>	0.1	8	0.3	19
Day hospital (visits) <sup>2</sup>	2.3	133	2.1	126
Community mental health centre (visits) <sup>2,3</sup>	2.4	44	1.4	25
Day care centre (visits) <sup>1</sup>	5.9	106	0.9	15
Group therapy <sup>2,3</sup>	0.4	6	0.1	2
Sheltered workshop <sup>3</sup>	1.1	45	0.0	0
Specialist education <sup>2,3</sup>	2.9	52	0.0	0
Other (not specified) <sup>3</sup>	0.6	12	0.0	0
Visits by				
Psychiatrist <sup>1</sup>	2.5	103	2.3	269
Psychologist <sup>3</sup>	0.0	0	0.0	2
General practitioner <sup>3</sup>	1.8	217	1.6	152
District nurse <sup>3</sup>	0.1	1	0.0	0
Community psychiatric nurse <sup>3</sup>	12.6	1014	5.2	791
Social worker <sup>3</sup>	0.1	24	0.4	106
Occupational therapist <sup>3</sup>	0.0	1	0.8	44
Home help/care worker <sup>3</sup>	0.4	0	0.6	0
Total costs <sup>1</sup>		1899		8212

# CONSEQÜÈNCIES DE LA RECAIGUDA

- Conseqüències del propi episodi (personal, familiar, situacions de risc)
- Impacte en la recuperació funcional (acadèmica, social)
- Major resistència al tractament
- Impacte econòmic ( major en psicosis no estable)
- S'han associat a alteracions cerebrals

*1- Emsley et al Sch Research 2013; 2. Almond et al. Br J Psychiatry 2004.*

# Focal Gray Matter Changes in Schizophrenia across the Course of the Illness: A 5-Year Follow-Up Study



Canvis frontals  
associats al n<sup>o</sup> d'  
hospitalitzacions

Menor canvis en tto  
amb olanzapina i  
clozapina

*1- Van Haren et al.  
Psychopharmacology  
2007*

## **Relapse Duration, Treatment Intensity, and Brain Tissue Loss in Schizophrenia: A Prospective Longitudinal MRI Study**

**Nancy C. Andreasen, M.D., Ph.D., Dawei Liu, Ph.D., Steven Ziebell, B.A., Anvi Vora, M.D., and Beng-Choon Ho, M.D.**

- Duració de la recaiguda associada a la pèrdua de volum cerebral total i substància gris frontal
- Intensitat del tractament (FGA i SGA) associada a disminució volum cerebral total

**Recaiguda 1.55 cc/any (0.99 F) vs Tractament 0.55 cc/any**



**Prevenió recaiguda amb mínim dosi eficaç mantinguda**

# Efecte diferencial atípics versus típics?

## **Atypical Neuroleptics Stimulate Neurogenesis in Adult Rat Brain**

Chandramohan G. Wakade,<sup>1,2</sup> Sahebarao P. Mahadik,<sup>3</sup> Jennifer L. Waller,<sup>4</sup> and Fung-chow Chiu<sup>1,2\*</sup>

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**Neurotoxic potential of haloperidol in comparison with risperidone: implication of Akt-mediated signal changes by haloperidol**

W. Ukai<sup>1</sup>, H. Ozawa<sup>2</sup>, M. Tateno<sup>1</sup>, E. Hashimoto<sup>1</sup>, and T. Saito<sup>1</sup>

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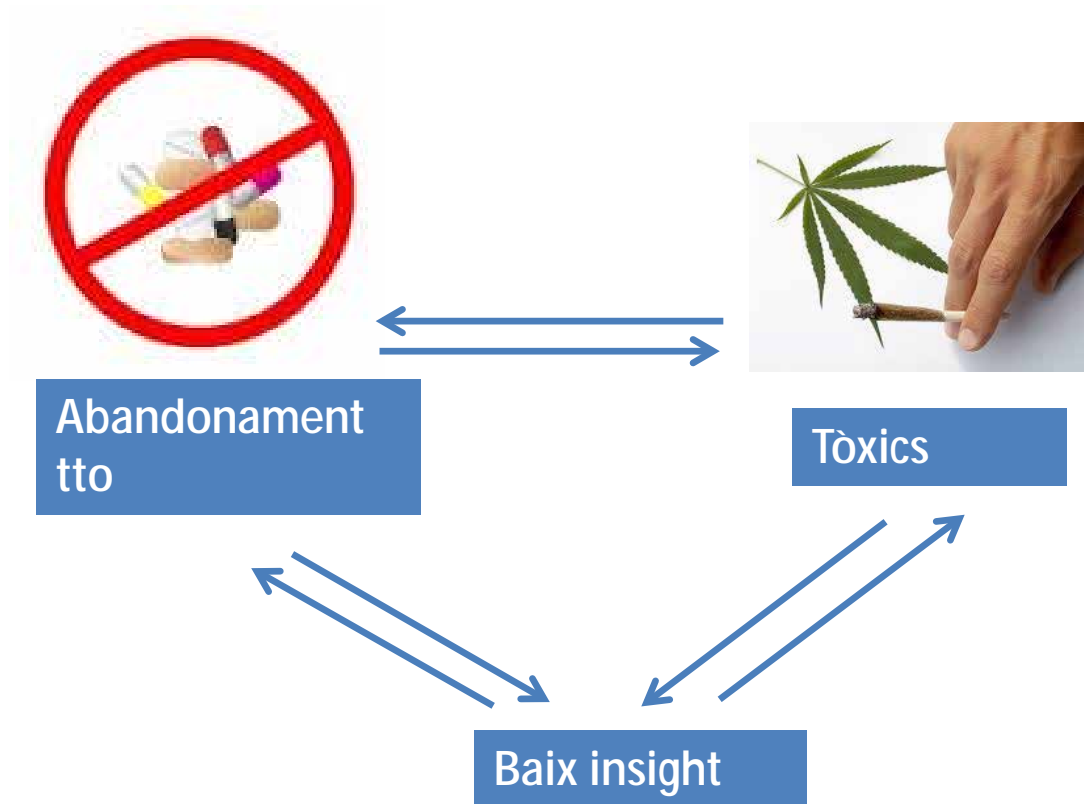
# Antipsychotic Drug Effects on Brain Morphology in First-Episode Psychosis

Jeffrey A. Lieberman, MD; Gary D. Tollefson, MD, PhD; Cecil Charles, PhD; Robert Zipursky, MD; Tommoy Sharma, MD; Rene S. Kahn, MD, PhD; Richard S. E. Keefe, PhD; Alan I. Green, MD; Raquel E. Gur, MD, PhD; Joseph McEvoy, MD; Diana Perkins, MD, MPH; Robert M. Hamer, PhD; Honglin Gu, PhD; Mauricio Tohen, MD, DrPH; for the HGDH Study Group

**Table 2. Changes in MRI Volumes for Primary Regions of Interest by Treatment Group (Baseline to Weeks 12, 24, 52, and 104)**

ROI	Therapy	Observed Case Mean Changes From Baseline and Mixed-Model <i>P</i> Values								
		Baseline		Week 12				Week 24		
		N	Mean (SE), cm <sup>3</sup>	N	Mean (SE), cm <sup>3</sup>	<i>P</i> Value*	<i>P</i> Value†	N	Mean (SE), cm <sup>3</sup>	<i>P</i> Value
WB	Olz	82	1155.01 (14.38)	73	4.74 (2.82)	.10	.66	65	2.30 (2.64)	.05
	Hal	79	1155.76 (13.16)	69	-3.26 (2.93)		.28	47	-6.22 (3.58)	
	Con	52	1181.93 (17.16)	52	1.74 (3.30)					
WBGm	Olz	82	683.99 (8.78)	73	2.65 (1.97)	.002	.93	65	-0.88 (2.05)	.002
	Hal	79	685.79 (8.23)	69	-5.85 (1.92)		.005	47	-10.36 (2.48)	
	Con	52	699.24 (10.29)	52	2.01 (2.28)					
WBWM	Olz	82	471.01 (5.98)	73	2.08 (1.88)	.39	.55	65	3.18 (2.22)	.63
	Hal	79	469.97 (5.38)	69	2.59 (2.23)		.17	47	4.13 (2.69)	
	Con	52	482.69 (7.33)	52	-0.28 (2.13)					
WBF	Olz	82	226.07 (4.05)	73	2.77 (1.55)	.14	.63	65	6.89 (1.42)	.56
	Hal	79	230.75 (3.87)	69	6.67 (1.80)		.18	47	5.70 (2.45)	
	Con	52	231.33 (4.78)	52	2.80 (2.51)					
LV	Olz	80	20.74 (0.97)	71	-0.05 (0.33)	.08	.86	64	-0.31 (0.36)	.27
	Hal	77	20.78 (1.29)	68	0.68 (0.33)		.01	46	0.62 (0.55)	
	Con	52	20.46 (1.18)	52	-0.28 (0.23)					
CN	Olz	80	8.89 (0.19)	71	-0.36 (0.13)	.12	.18	64	-0.23 (0.15)	.03
	Hal	77	8.62 (0.15)	68	0.03 (0.13)		.92	46	-0.04 (0.14)	
	Con	52	9.09 (0.16)	52	-0.01 (0.15)					

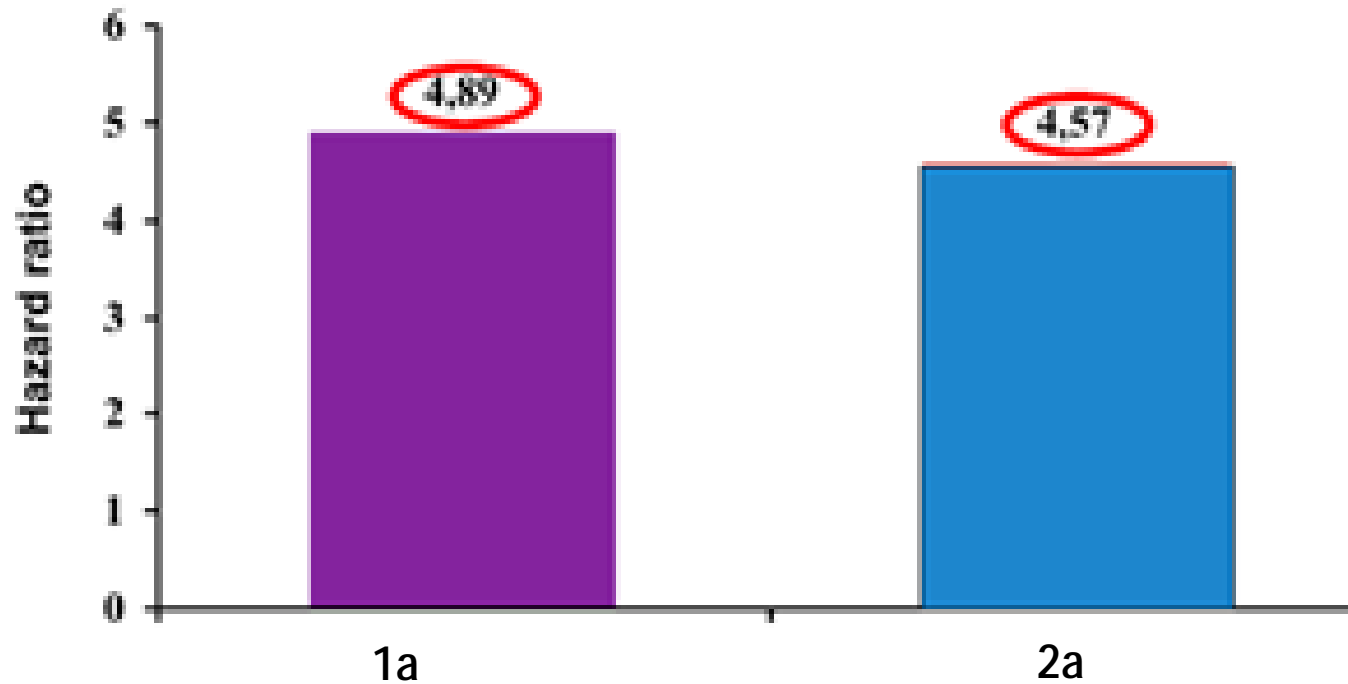
# FACTORS DE RISC DE RECAIGUDA



*Thomas P. Encephale  
2013*



# INCUMPLIMENT AUGMENTA EL RISC DE RECAIGUDA

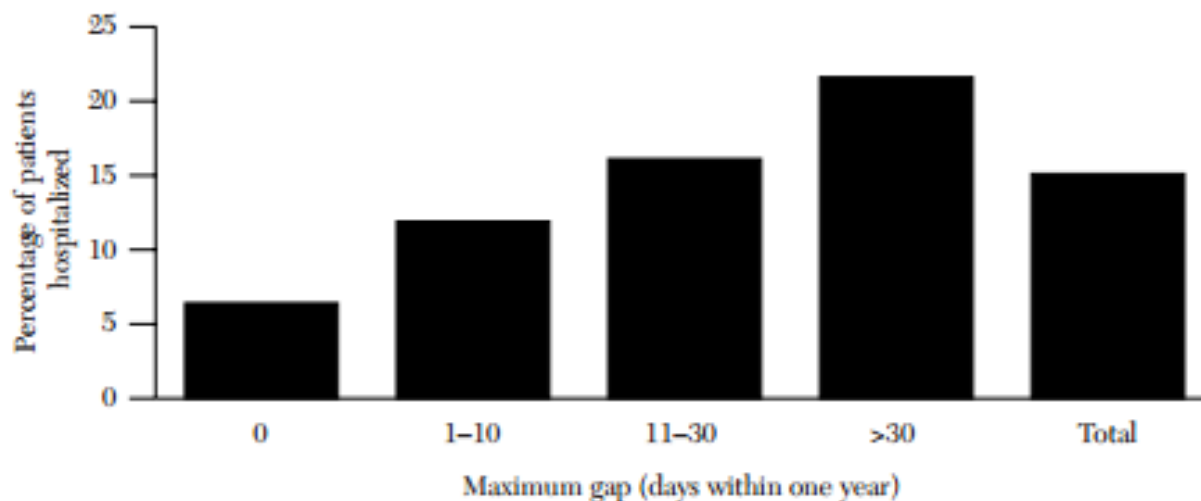


# Partial Compliance and Risk of Rehospitalization Among California Medicaid Patients With Schizophrenia

Peter J. Weiden, M.D.  
Chris Kozma, Ph.D.  
Amy Grogg, Pharm.D.  
Julie Locklear, Pharm.D., M.B.A.

**Figure 1**

Percentage of patients with schizophrenia who were rehospitalized, by maximum gap in therapy<sup>a</sup>



OR hospitalització

1-10	1.98
11-30	2.81
>30	3.96

# INCOMPLIMENT A L'ESQUIZOFRÈNIA

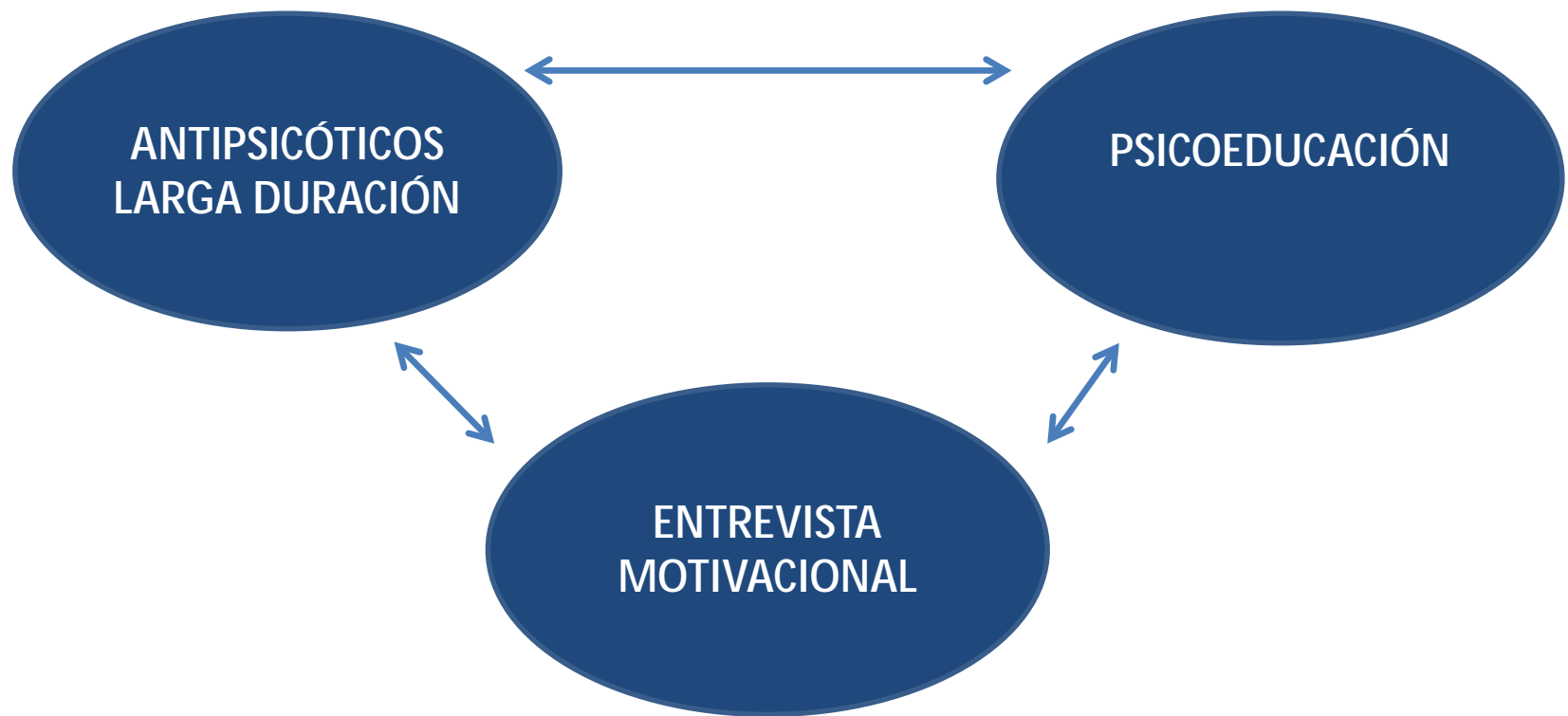
Prevalença de 50% (4-72%)

Factors de risc :

- Relacionats amb pacient: edat, gènere masculí, símptomes positius, negatius i cognitius, **baix insight, consum tòxics**
- Ambientals: Pobre suport social, dificultats accés recursos sanitaris
- Relacionats amb el metge: mala relació terapèutica, inadequada planificació tractament, poca psicoeducació pacient i familiars
- Relacionats amb el tractament: posologia complicada, ineficàcia, efectes secundaris

# Estratègies per evitar recaigudes

# Estrategias de actuación para mejorar adherencia

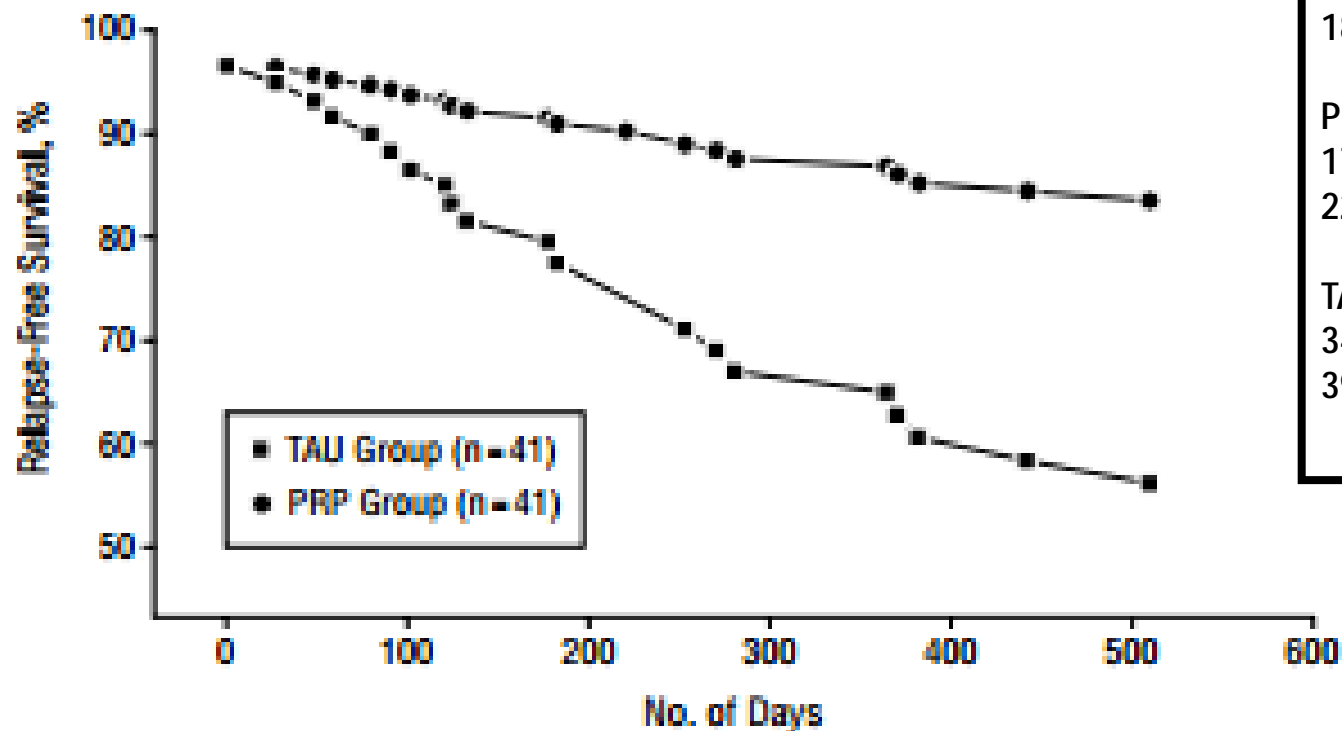


1. Herz MI Arch Gen Psychiatry 2000. 2- Acosta et al World J Psychiatry 2012. 3- Barkhof et al Sch Bulletin 2013

# A Program for Relapse Prevention in Schizophrenia

## A Controlled Study

Marvin I. Herz, MD; J. Steven Lamberti, MD; Jim Mintz, PhD; Ruth Scott, MS, RN, CS;  
Susan P. O'Dell, MS, RN, CS; Lisa McCartan, MA; Glen Nix, PhD



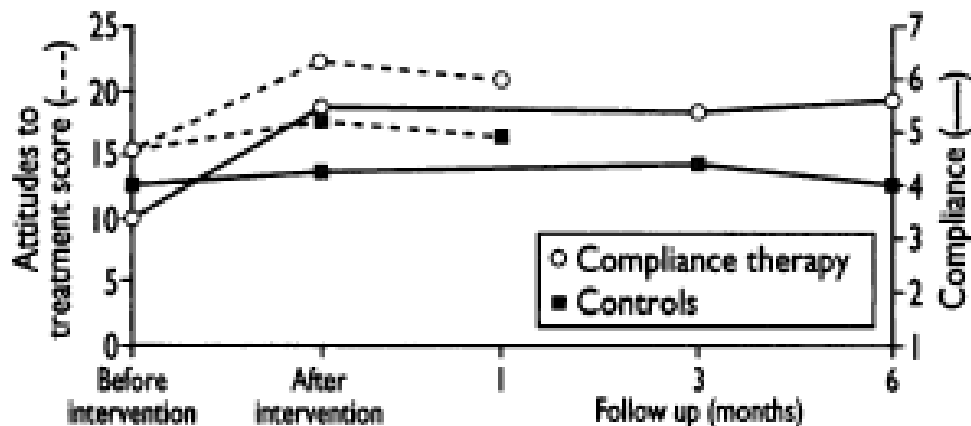
18 MESOS

PRP  
17% Recaigudes  
22% Hospitalitzacions

TAU  
34% Recaigudes  
39% Hospitalitzacions

# Compliance therapy in psychotic patients: randomised controlled trial

Roisin Kemp, Peter Hayward, Grantley Applewhaite, Brian Everitt, Anthony David



**Fig 1**—Attitudes to treatment (drug attitudes inventory) and compliance over time in patients receiving compliance therapy or non-specific counselling (controls)

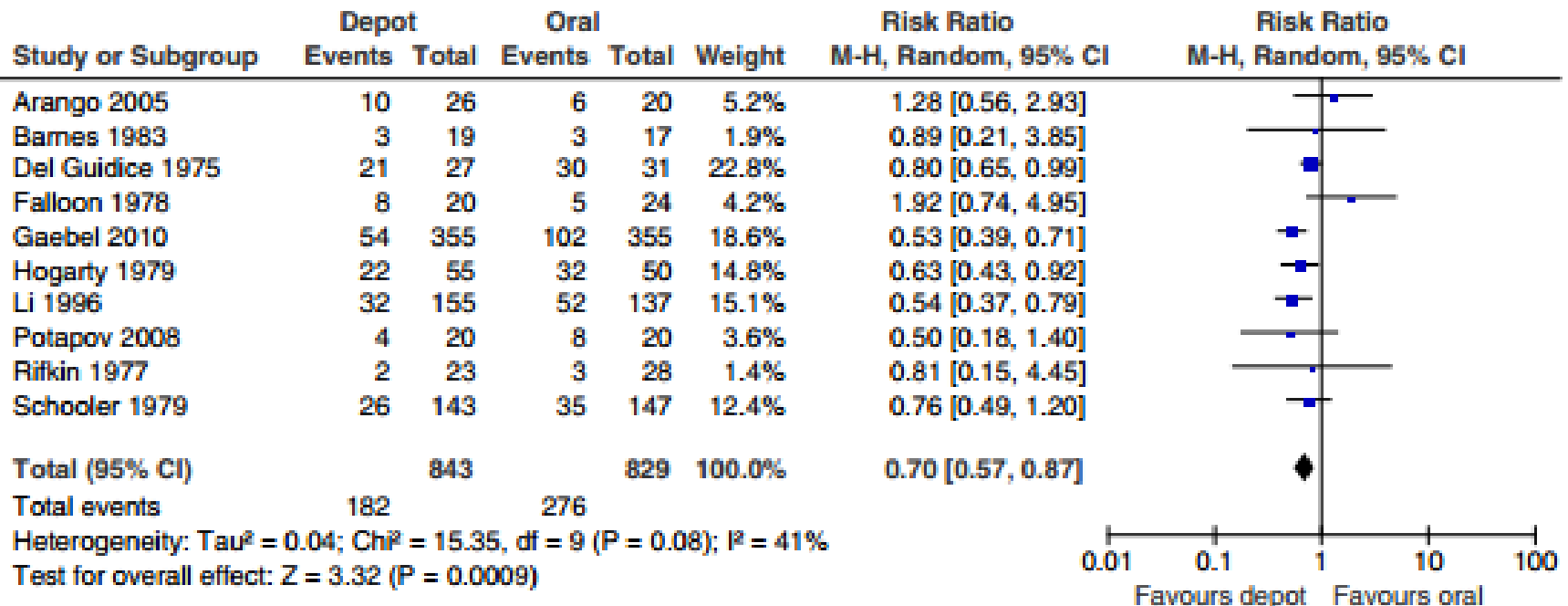
# Antipsicòtics de llarga durada

- Facilita compliment
- **Transparència immediata del no compliment**
- Dosi mes estable en sang (evitant pic-vall)
- Facilita contacte freqüent amb equip assistencial



## Oral versus depot antipsychotic drugs for schizophrenia—A critical systematic review and meta-analysis of randomised long-term trials

Claudia Leucht<sup>a</sup>, Stephan Heres<sup>a</sup>, John M. Kane<sup>c</sup>, Werner Kissling<sup>a</sup>, John M. Davis<sup>b</sup>, Stefan Leucht<sup>a,\*</sup>



# Long-Acting Injectable vs Oral Antipsychotics for Relapse Prevention in Schizophrenia: A Meta-Analysis of Randomized Trials

Taishiro Kishimoto<sup>1,2</sup>, Alfred Robenzadeh<sup>1</sup>, Claudia Leucht<sup>3</sup>, Stefan Leucht<sup>3</sup>, Koichiro Watanabe<sup>2,4</sup>, Masaru Mimura<sup>2</sup>, Michael Borenstein<sup>5</sup>, John M. Kane<sup>1,6,7,8</sup>, and Christoph U. Correll<sup>\*,1,6,7,8</sup>

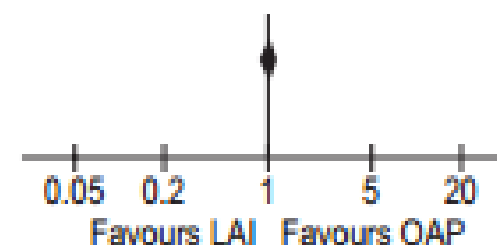
Total (95% CI)                      2556                      2326    100.0%                      1.03 [0.90, 1.18]

Total events                      963                      908

Heterogeneity:  $\text{Tau}^2 = 0.04$ ;  $\text{Chi}^2 = 44.31$ ,  $df = 19$  ( $P = 0.0009$ );  $I^2 = 57\%$

Test for overall effect:  $Z = 0.45$  ( $P = 0.65$ )

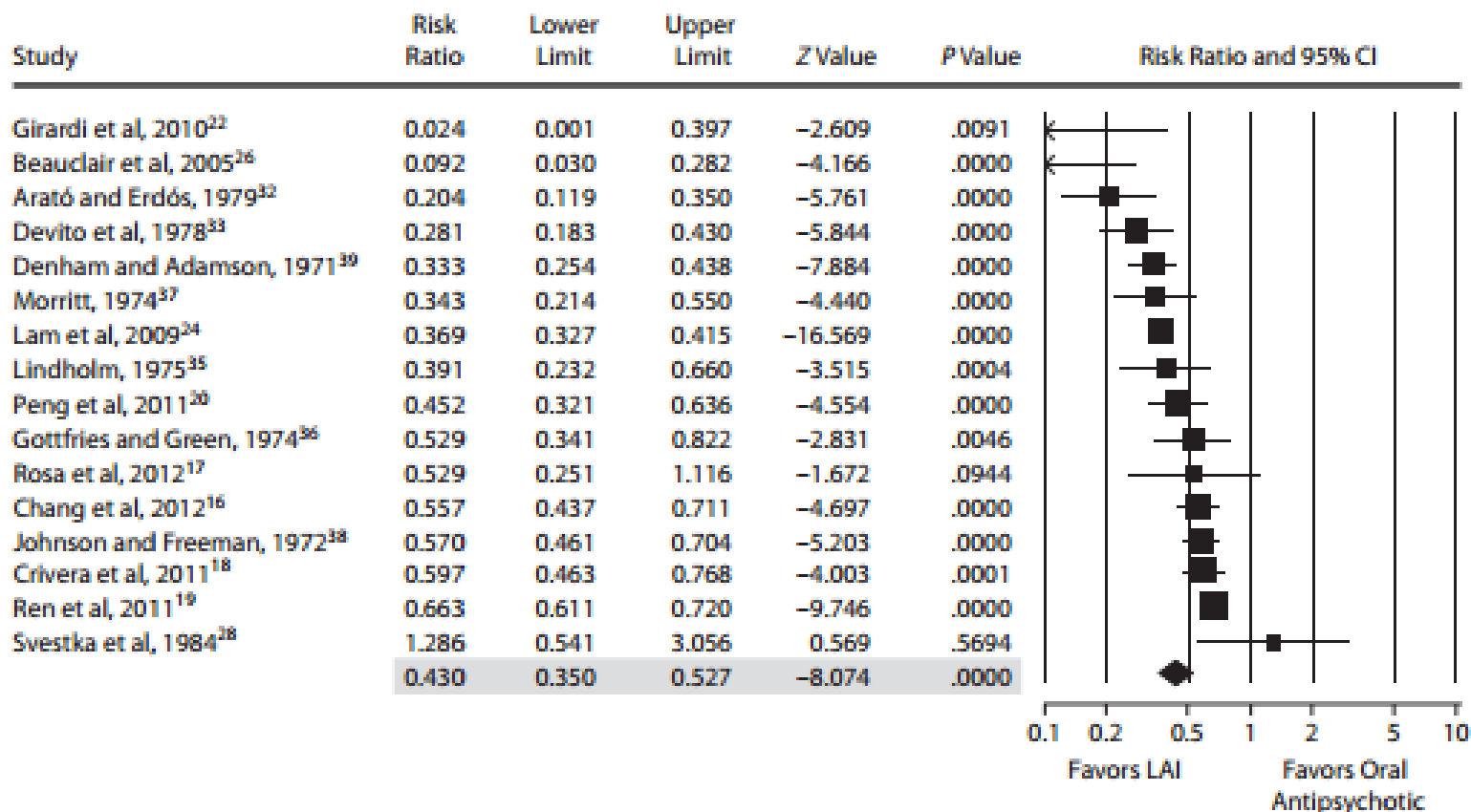
Test for subgroup differences:  $\text{Chi}^2 = 2.29$ ,  $df = 4$  ( $P = 0.68$ ),  $I^2 = 0\%$



# Long-Acting Injectable Versus Oral Antipsychotics in Schizophrenia: A Systematic Review and Meta-Analysis of Mirror-Image Studies

Taishiro Kishimoto, MD; Masahiro Nitta, MS;  
Michael Borenstein, PhD; John M. Kane, MD; and Christoph U. Correll, MD

Figure 2. Hospitalization Risk



# Evolució tractaments antipsicòtics

50s

60s

70s

90s

00

10

↑  
Clorpromazina

↑  
Haloperidol  
Flufenazina  
Tiordazina  
Loxapina  
Perfenazina

↑  
Flufenazina decanoat

↑  
Clozapina

↑  
Zuclopentixol decanoat

↑  
Risperidona  
Olanzapina  
Quetiapina  
Ziprasidona

↑  
Risperidone long acting

↑  
Aripiprazol  
Paliperidona

↑  
Olanzapine pamoat  
Paliperidone palmitat  
Aripiprazol long acting injection

↑  
asenapina

# LAI disponibles

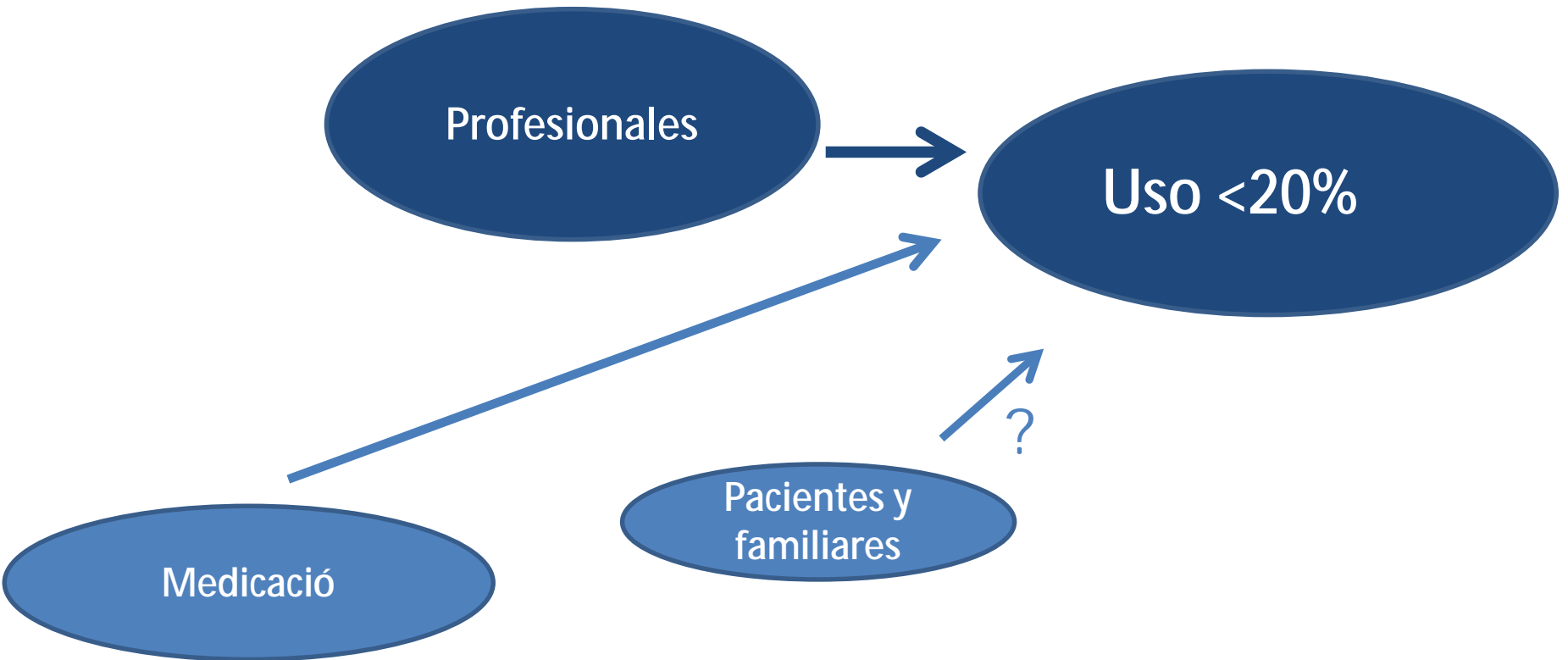
	Emmagatzament	Administració	Efectes secundaris
Flufenazina decanoat	Suspensió oliosa	2-5 setmanes	Simptomes extrapiramidals, somnolència
Zuclopentixol decanoat	Suspensió oliosa	2-4 setmanes	Simptomes extrapiramidals, somnolència
Risperidona llarga durada	Microsfera en solució aquosa	Quinzenal. Precisa refrigeració previa i suplementació oral.	Cefalea, s.extrapiramidals, mareig, acatisia, sedació, augment de pes, dolor extremitats
Olanzapina pamoat	Solució aquosa	2-4 setmanes. Administració hospitalaria (3h). Síndrome postinjecció.	Sedació, augment de pes, vòmits, diarrea, cefalea
Paliperidona Palmitat	Solució aquosa	Mensual. Inici Injecció dia 1 i 8	Dolor al lloc de la injecció, mareig somnolència, parkinsonisme, acatisia
Aripiprazol llarga durada	Solució aquosa	Precisa suplementació oral	Acatisia

# Elecció?

Individualitzat. Considerar:

- Resposta prèvia
- Perfil efectes secundaris
- Interaccions
- Preu (estudis cost-eficàcia llarg plaç necessaris)

# Barreras



1-Kane J-. *Jclin psy*  
2014. 2- Kirchner et al  
*Am Clin Psychiatry*  
2013

# CONCLUSIONS

Les recaigudes en els pacients amb esquizofrènia tenen greus conseqüències personals, socials, laborals, cerebrals, pronòstiques

L' incompliment del tractament es un dels principals determinants de la recaiguda

La combinació de psicoeducació, entrevista motivacional, antipsicòtics de llarga durada permet millorar l'adherència

Els antipsicòtics de llarga durada han mostrat efectivitat en la disminució de les recaigudes, tot i això, encara són poc utilitzats, en part pels propis professionals i les limitacions en disponibilitat.

Son necessaris més estudis farmacoeconòmics a llarg plaç dels diferents LAI i antipsicòtics orals





## Comparative Effectiveness of Risperidone Long-Acting Injectable vs First-Generation Antipsychotic Long-Acting Injectables in Schizophrenia: Results From a Nationwide, Retrospective Inception Cohort Study.

Nielsen J<sup>1</sup>, Jensen SO<sup>2</sup>, Friis RB<sup>2</sup>, Valentin JB<sup>2</sup>, Correll CU<sup>3</sup>.

### ⊕ Author information

### Abstract

**OBJECTIVE:** To compare in a generalizable sample/setting objective outcomes in patients receiving first-generation antipsychotic long-acting injectables (FGA-LAIs) or risperidone-LAI (RIS-LAI).

**METHODS:** Nationwide, retrospective inception cohort study of adults with International Classification of Diseases-10 schizophrenia using Danish registers from 1995 to 2009 comparing outcomes between clinician's/patient's choice treatment with FGA-LAIs or RIS-LAI. Primary outcome was time to psychiatric hospitalization using Cox-regression adjusting for relevant covariates. Secondary outcomes included time to all-cause discontinuation and psychiatric hospitalization in patients without LAI possession gap >28 days, and number of bed-days after psychiatric hospitalization.

**RESULTS:** Among 4532 patients followed for 2700 patient-years, 2078 received RIS-LAI and 2454 received FGA-LAIs (zuclopenthixol decanoate = 52.2%, perphenazine decanoate = 37.2%, haloperidol decanoate = 5.0%, flupenthixol decanoate = 4.4%, fluphenazine decanoate = 1.3%). RIS-LAI was similar to FGA-LAIs regarding time to hospitalization (RIS-LAI = 246.2±323.7 days vs FGA-LAIs = 276.6±383.3 days; HR = 0.95, 95% confidence interval (CI) = 0.87-1.03, P = 0.199) and time to all-cause discontinuation (RIS-LAI = 245.8±324.0 days vs FGA-LAIs = 287.0±390.9 days; HR = 0.93, 95% CI = 0.86-1.02, P = 0.116). Similarly, in patients without LAI discontinuation, RIS-LAI and FGA-LAIs did not differ regarding time to hospitalization (RIS-LAI = 175.0±268.1 days vs FGA-LAIs = 210.7±325.3 days; HR = 0.95, 95% CI = 0.86-1.04, P = 0.254). Finally, duration of hospitalization was also similar (incidence rate ratio = 0.97, 95% CI = 0.78-1.19, P = 0.744). Results were unchanged when analyzing only patients treated after introduction of RIS-LAI.

**CONCLUSIONS:** In this nationwide cohort study, RIS-LAI was not superior to FGA-LAIs regarding time to psychiatric hospitalization, all-cause discontinuation, and duration of hospitalization. Given the cost of hospitalization and second-generation antipsychotic (SGA)-LAIs, these findings require consideration when making treatment choices, but also need to be balanced with the individual relevance of adverse effects/patient centered outcomes. In future, head-to-head trials and additional nationwide database studies including other SGA-LAIs is needed.

# Decline in hospitalization risk and health care cost after initiation of depot antipsychotics in the treatment of schizophrenia

This article was published in the following Dove Press journal:

ClinicoEconomics and Outcomes Research

10 January 2011

[Number of times this article has been viewed](#)

Xiaomei Peng  
Haya Ascher-Svanum  
Douglas Faries  
Robert R Conley  
Kory J Schuh

Eli Lilly and Company, Indianapolis,  
IN, USA

**Purpose:** To assess change in hospitalization and cost of care from 6 months pre- to 6 months post-initiation on any depot antipsychotic among schizophrenia patients.

**Patients and methods:** Using a large United States commercial claims and encounters database, patients younger than 65 years diagnosed with schizophrenia were identified. Patients initiated on a depot antipsychotic were studied in a mirror-image design to assess change in hospitalization rates, mean duration hospitalized, and hospitalization cost. McNemar's test and paired *t*-tests compared the proportions of patients hospitalized and the mean duration. Paired *t*-test and bootstrapping methods compared costs.

**Results:** In these patients ( $n = 147$ ), psychiatric hospitalizations declined from 49.7% pre-initiation to 22.4% post-initiation ( $P < 0.001$ ), and the mean hospitalized duration for psychiatric purposes numerically declined from 7.3 to 4.7 days ( $P = 0.05$ ). Total health care costs declined from \$11,111 to \$7884 ( $P < 0.05$ ) driven by reduction in costs for psychiatric hospitalizations from \$5384 to \$2538 ( $P < 0.05$ ).

**Conclusion:** Initiation of depot antipsychotic therapy appeared to be associated with a decline in hospitalization rates and costs. Current findings suggest that treatment with depot antipsychotics may be a cost-effective option for a subgroup of patients with schizophrenia who are at high risk of nonadherence with their oral antipsychotic medication regimen.