Treatment of Schizophrenia Across the Illness Stages

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Disclosures: Christoph U. Correll

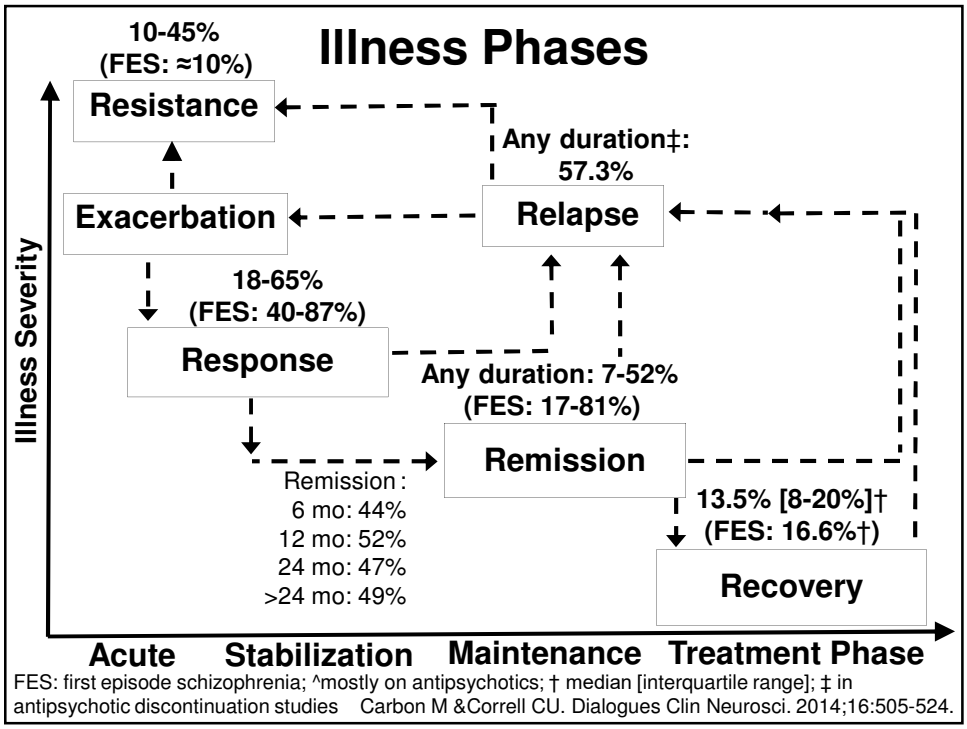
I have an interest in relation with one or more organizations that could be perceived as a possible conflict of interest in the context of this presentation. The relationships are summarized below:

Interest	Name of organization
Grants	Bendheim Foundation, Janssen, National Institute of Mental Health (NIMH), Patient Centered Outcomes Research Institute (PCORI), Takeda, Thrasher Foundation
Shares	No share holdings in pharmaceutical companies
Paid positions, honoraria and advisory boards	Alkermes, Angelini, Bristol-Myers Squibb, Forum, Gerson Lehrman Group, IntraCellular Therapies, Janssen/J&J, LB Pharma, Lundbeck, Medavante, Medscape, Neurocrine, Otsuka, Pfizer, ProPhase, ROVI, Sunovion, Supernus, Takeda, and Teva

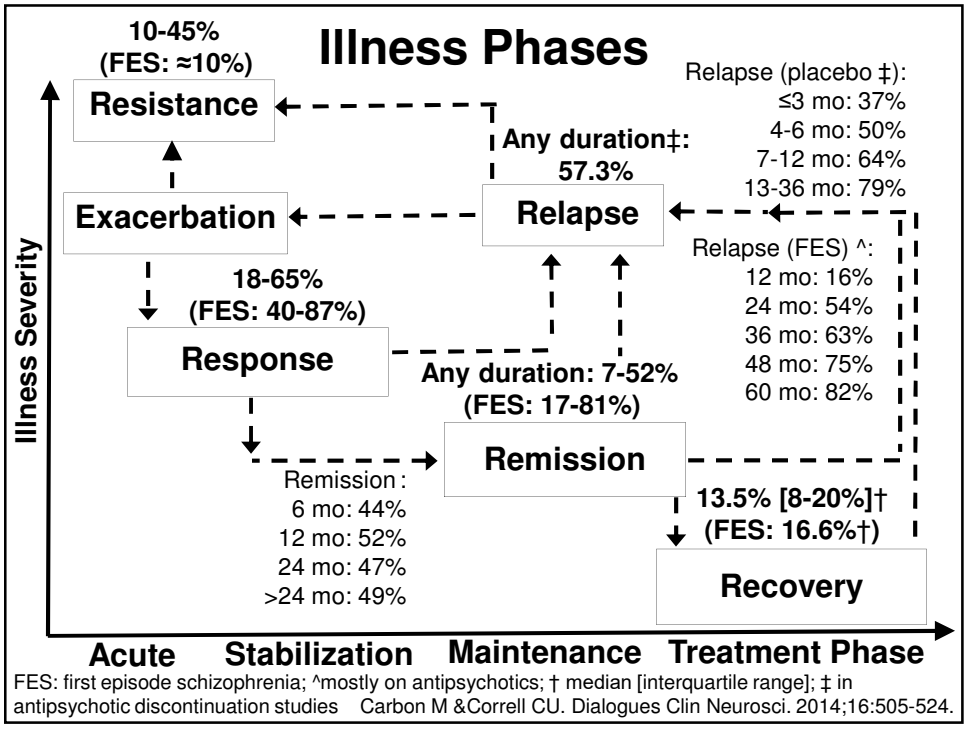
Overview

- Treatment Goals
- Acute Treatment
- Maintenance Treatment/Relapse Prevention
- What is the Role of LAIs?
- What is the Role of LAIs in the Treatment of Early Episode Patients?
- Adverse Effects
- Offering LAIs
- Conclusions

Treatment Goals



FES: first episode schizophrenia; ^mostly on antipsychotics; † median [interquartile range]; ‡ in antipsychotic discontinuation studies Carbon M &Correll CU. Dialogues Clin Neurosci. 2014;16:505-524.



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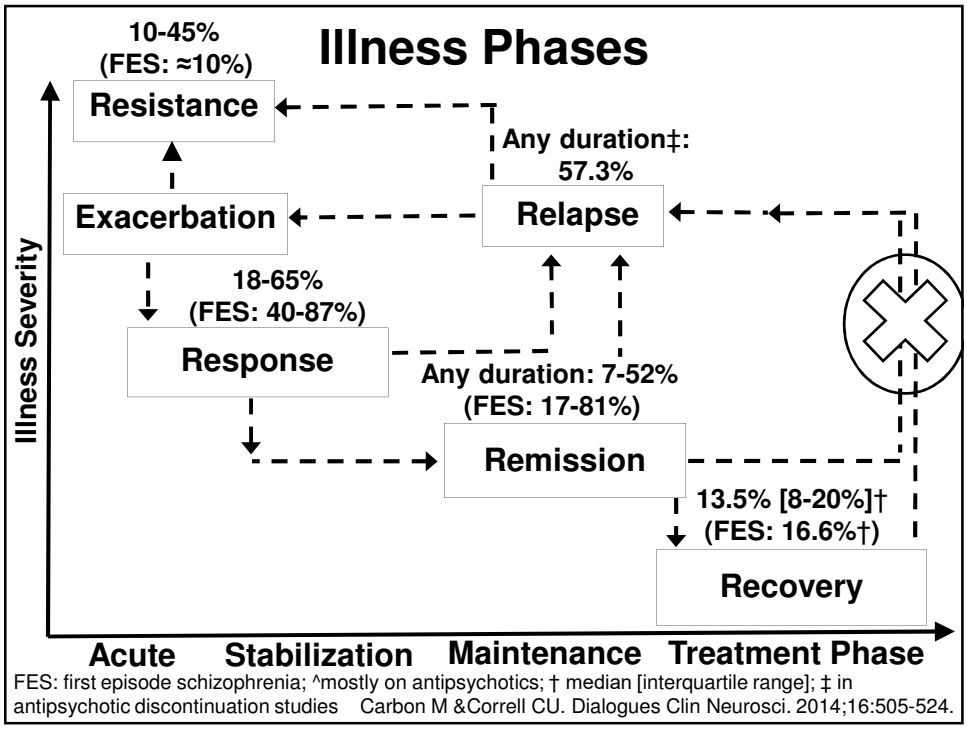

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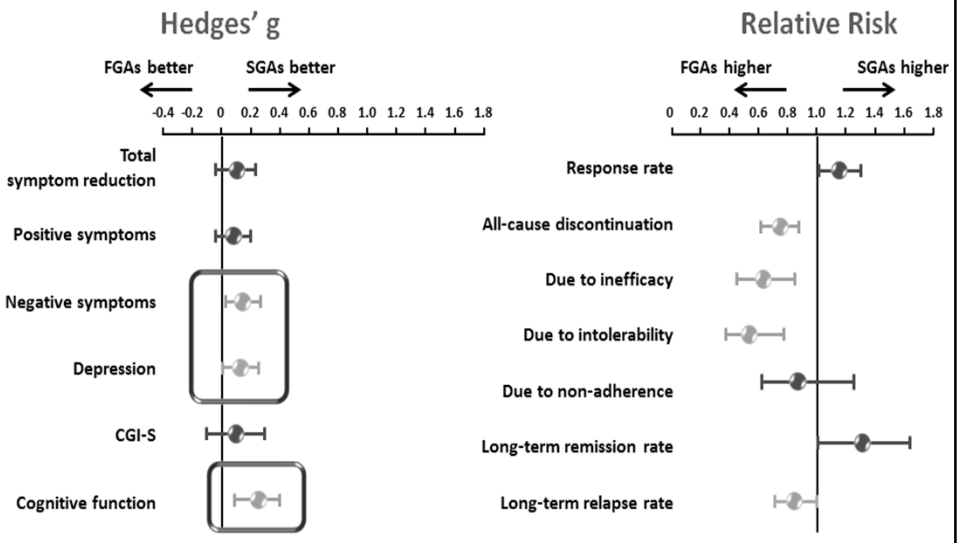
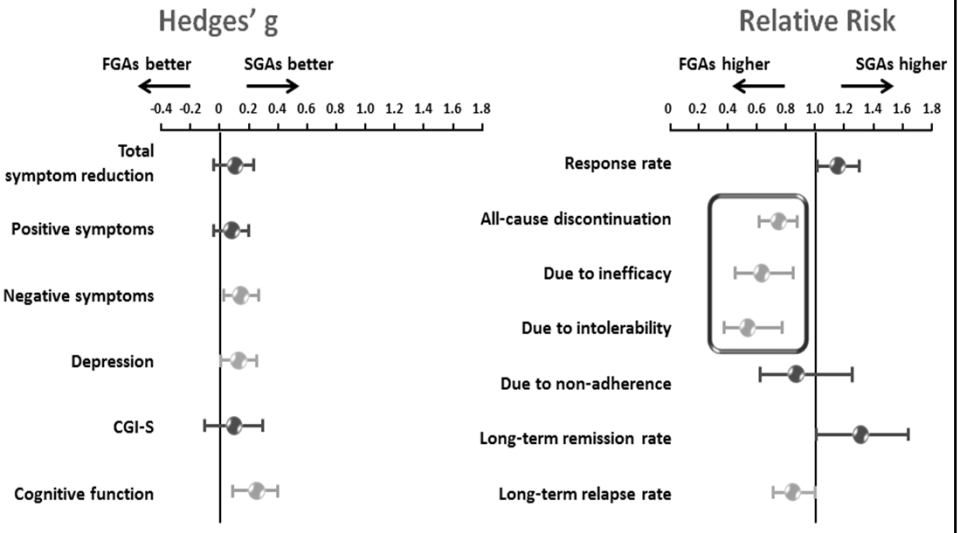
Acute Treatment

Randomized Trials of SGAs vs FGAs in First-Episode Schizophrenia (N=13, n=2519)



Zhang JP, Gallego J, Robinson D, Malhotra AK, Kane JM, Correll CU. Int J Neuropsychopharm. 2013 Jul;16(6):1205-18.

Randomized Trials of SGAs vs FGAs in First-Episode Schizophrenia (N=13, n=2519)



Zhang JP, Gallego J, Robinson D, Malhotra AK, Kane JM, Correll CU. Int J Neuropsychopharm. 2013 Jul;16(6):1205-18.

1st Episode Schizophrenia: Key Points

- First episode patients are generally more treatment responsive
- They require lower doses
- They are more sensitive to side effects
- Relapse is very common
- While acute efficacy might be similar with FGAs and SGAs, relapse and treatment discontinuation seem to be higher with FGAs
- Multidisciplinary interventions, focusing on engagement, treatment continuation, relapse prevention, physical health and functional recovery are paramount

Multiple Treatments Meta-analysis of Acute Efficacy of Antipsychotics vs. Placebo in Non-refractory Schizophrenia

Aim

- Create hierarchy for 15 antipsychotic drugs
- Efficacy and major side-effects
- Direct and indirect comparisons
- Includes some treatments without an EU license for Schizophrenia (Sertindole*, iloperidone*, zotepine*, ziprazidone*, asenapine)

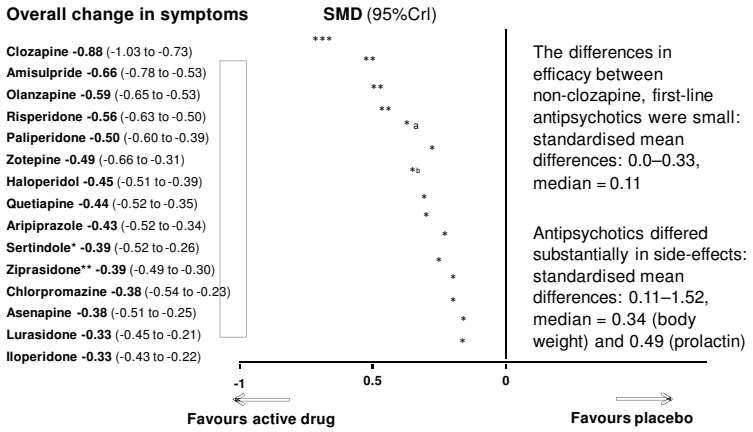
Data set

- 212 randomised controlled trials
- Acute schizophrenia
- 43,049 participants
- Mean illness duration: 12.4 yrs
- Mean age: 38.4 yrs

Network of comparisons for efficacy

*Not licensed for use in the UK.
Leucht S et al. *Lancet* 2013; 382(9896): 951-62.

Acute Efficacy of Antipsychotics vs. Placebo in Non-refractory Schizophrenia



The differences in efficacy between non-clozapine, first-line antipsychotics were small: standardised mean differences: 0.0–0.33, median = 0.11

Antipsychotics differed substantially in side-effects: standardised mean differences: 0.11–1.52, median = 0.34 (body weight) and 0.49 (prolactin)

Zotepine, Ziprasidone, Sertindole, Iloperidone not licensed for use in the UK

1, 2 or 3 asterisks: *significant separation from placebo; ** significant separation from agents with one asterisk; *** significant separation from all other agents; a: only superior to lurasidone and iloperidone; b: only superior to iloperidone; SMD +/- 95% Cis.
Leucht S et al. *Lancet* 2013; 382(9896): 951-62.

Maintenance Treatment & Relapse Prevention

What is the Importance of Relapse Prevention?

1. Harrison G et al. *Br J Psychiatry.* 2001;178(6): 506-517. 2. Herings RM, Erkens JA. *Pharmacoepidemiol Drug Saf 2003*;12(5):423-424. 3. Lieberman JA et al. *Neuropsychopharmacology* 1996; 14:13S-21S. 4. Andreasen N et al. *Am J Psychiatry* 2013;170: 609-15. 5. Kane JM. *J Clin Psychiatry* 2007; 68(Suppl 14): 27–30.

Clinical Predictors of Poor Outcomes in the Long-Term Course of First-Episode Schizophrenia*

Fixed Risk Factors	Modifiable Risk Factors
Male sex	Longer duration of untreated psychosis
Earlier illness onset	Comorbidities (eg, addiction)
Premorbid developmental delay	Early nonresponse to antipsychotic medication
Longer illness duration	Greater number of relapses ↕ Nonadherence
More severe illness	

*Based on longitudinal first episode samples
Carbon M and Correll CU. Dialogues Clin Neurosci. 2014;16:505-524.

Antipsychotics vs placebo for Relapse Prevention in SCZ

Depot APs reduced relapse (RR 0·31, 95% CI 0·21–0·41) more than oral drugs (0·46, 0·37–0·57; p=0·03). In a meta-regression, drug-pbo advantages decreased with study length.

Leucht S et al. *Lancet* 2012; 379(9831): 2063-71.

APs vs PBO for Relapse Prevention in SCZ

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Memory Aids….

Indirect comparison: LAIs and oral APs compared with placebo for relapse prevention

Relapse at 7–12 months	Patients, n	Studies, n	Risk ratio (95% CI)
LAI studies	663	7	0.31 (0.23–0.41)
Oral studies	1,785	14	0.46 (0.37–0.57)

Favours drug | Favours placebo

Test for subgroup differences: p=0.03, I^2=77.9%

AP, antipsychotic; CI, confidence interval; LAI, long-acting injectable antipsychotic.
Leucht S et al. *Lancet* 2012; 379(9831): 2063-71.

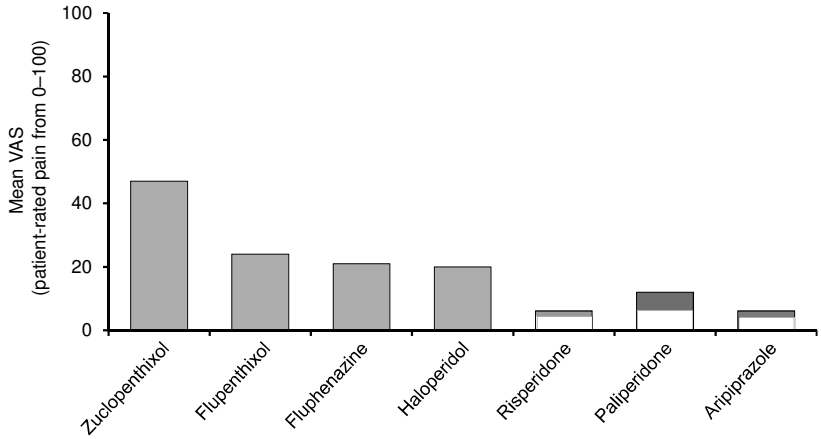
What is the Role of LAIs?

Characteristics of Selected 1st and 2nd Generation LAIs

Antipsychotic	Base	Dose Interval	Dosage Strengths/Forms	Starting Dose	Maintenance Dose	Oral Supplementation	Time to Peak	Steady State	Postinjection Observation
Fluphenazine decanoate[81]	Oil	Varies	25 and 100 mg/mL ampoules/vials/syringes	Varies, 12.5 mg	Varies, 12.5–100 mg	No	2–4 d	2–3 mo	No
Haloperidol decanoate[82] (Haldol and others)	Oil	4 wk	50 and 100 mg/mL ampoules	Varies, 50 mg	Varies, 300 mg	No	6–7 d	2–3 mo	No
Risperidone microspheres[83] (Risperdal Consta)	Water	2 wk	25, 37.5, 50 mg vial kits	25 mg	25 mg (25–50 mg)	3 wk	4–6 wk	1.5–2 mo	No
Olanzapine pamoate[84] (Zyprexa Relprevv)	Water	2 or 4 wk	210, 300, 405 mg vial kits	Varies, up to 300 mg/ 2 wk	Varies, up to 300 mg/ 2 wk	No	4 d	3 mo	At least 3 hours
Paliperidone palmitate LAI[85] (Invega Sustenna)	Water	Monthly	78, 117, 156, 234 mg prefilled syringes	150 mg (day 1) + 100 mg (day 8)	75 mg (25–150 mg)	No	13 d	7–11 mo	No
Paliperidone palmitate LAI[86] (Invega Trinza)	Water	Once every 3 mo	273, 410, 546, 819 mg prefilled syringes	Depending on once-monthly dose	Varies, 273–819 mg	No	30–33 d	Continues steady state at equivalent dose	No
Aripiprazole monohydrate[87] (Abilify Maintena)	Water	Monthly	300, 400 mg vial kits and dual-chamber syringe	400 mg	400 mg (300–400 mg)	2 wk	5–7 d	400: 4–8 mo; 300: 3–4 mo	No
Aripiprazole lauroxil[88] (Aristada)	Water	Monthly (or 6 weekly: 882 mg)	441, 662, 882 mg prefilled syringes	Varies, 441–882 mg	Varies, 441–882 mg	3 wk	4 d	4–6 mo	No

Correll CU et al. J Clin Psychiatry. 2016;77(suppl 3):1-24.

Subject ratings of LAI injection site pain rated on a visual analogue scale (VAS)

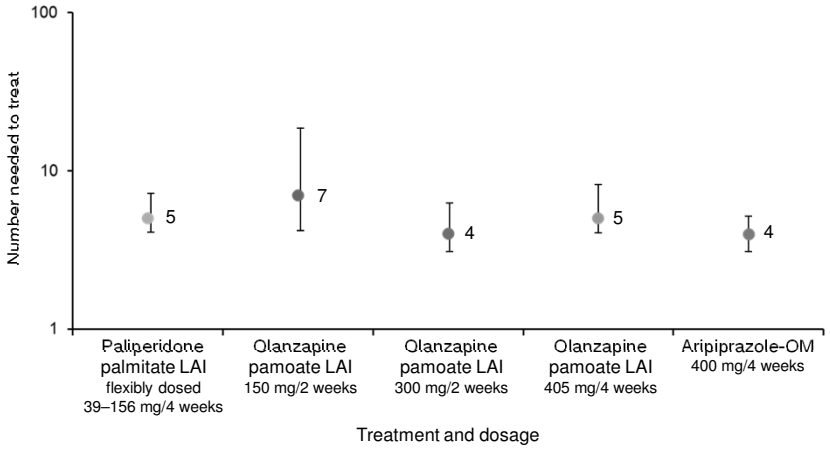


Data combined from various different studies using different methodologies; no direct comparison can be made; data from Bloch et al., were rated on a 0–10 VAS scale, so equivalents shown here; LAI=long-acting injectable

Adapted from Bloch et al. J Clin Psychiatry 2001;62(11):855–859; Quiroz et al. Innov Clin Neurosci 2011;8:20–28; Gopal et al. J Psychopharmacol 2011; 25(5):685–697; Kane et al. J Clin Psychiatry 2012;73(5):617–624

Prevention of relapse with selected LAIs vs placebo

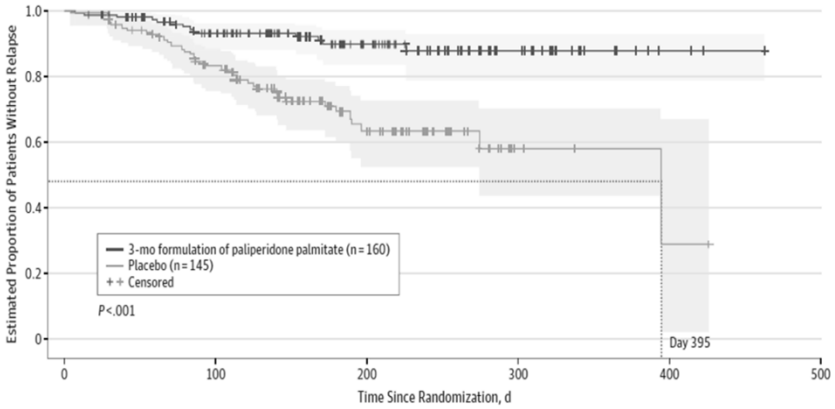
(vs 45 mg/4 weeks olanzapine pamoate for OLA-LAI)



OLA=olanzapine; LAI=long-acting injectable; OM=once-monthly

Citrome. Expert Rev Neurother 2013;13(7):767–783

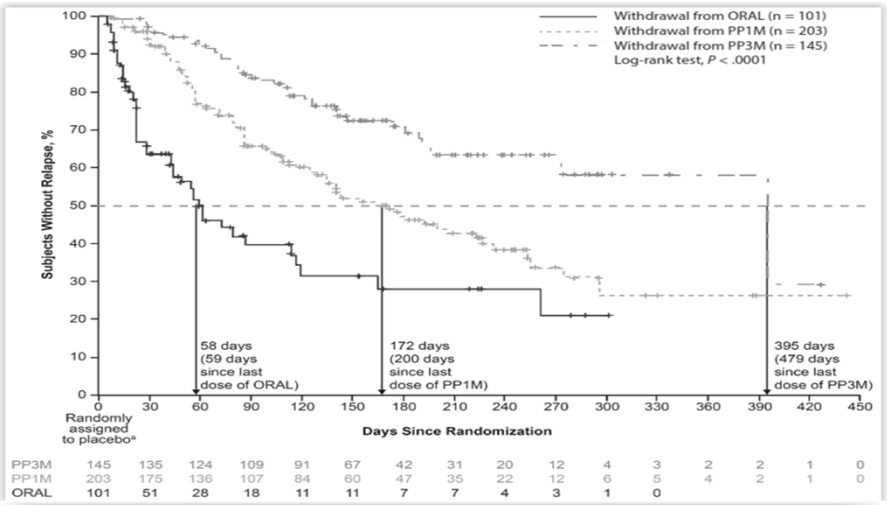
3-Monthly Paliperidone LAI vs PBO: Significantly Longer Time to Relapse



Time, d	0	30	60	90	120	150	180	210	240	270	300	330	360	390	420	450
No. of Patients Left																
3-mo formulation of paliperidone palmitate	160	151	143	131	121	93	67	47	30	22	17	10	7	4	2	1
Placebo	145	134	124	108	91	66	41	29	20	12	4	3	2	2	1	0

Berwaerts J, et al. JAMA Psychiatry. 2015 Aug;72(8):830-9. .

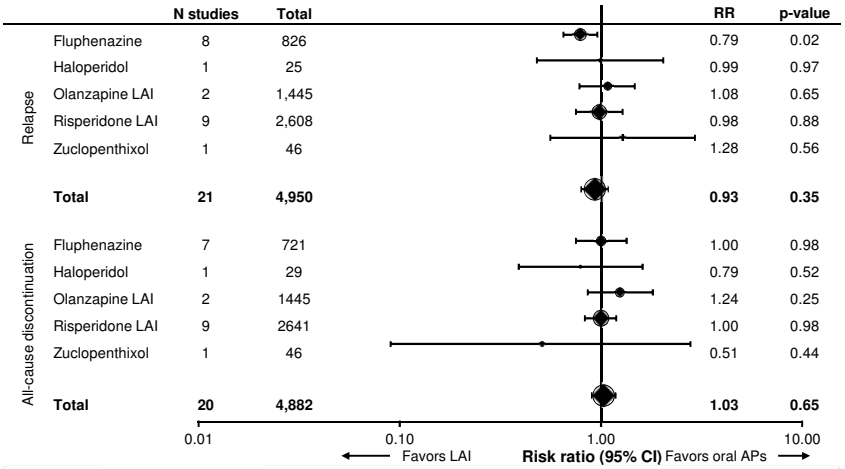
Time to relapse after switch to PBO after stabilization on PALI once daily (ORAL), monthly (PP1M), or 3 monthly (PP3M)



Variable	Placebo Arms		
	PP1M vs ORAL	PP3M vs ORAL	PP3M vs PP1M
Unadjusted HR (95% CI)[a]	0.441 (0.313–0.620)	0.212 (0.140–0.320)	0.480 (0.334–0.691)
P value	< .0001	< .0001	.0001

Weiden PJ et al. J Clin Psychiatry. 2017 Jul;78(7):e813-e820.

No differences in study-defined relapse/all-cause discontinuation between LATIs and oral antipsychotics



No difference in adherence between pooled LAIs and oral APs (measured in 10 studies)

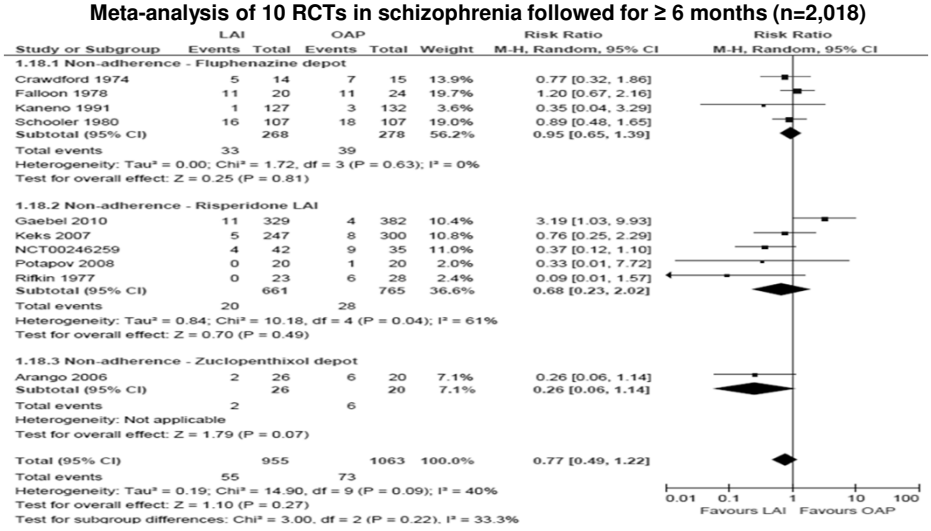
AP, antipsychotic; CI, confidence interval; LAT, long-acting treatment; RR, relative risk

21 studies, n=5176

Kishimoto T, Robenzadeh A, Leucht C, Leucht S, Watanabe K, Mimura M, Borenstein M, Kane JM, Correll CU. Schizophr Bull 2014 Jan;40(1):192-213.

In RCTs, LATs Were not Superior to Oral Antipsychotics Regarding Adherence

Meta-analysis of 10 RCTs in schizophrenia followed for ≥ 6 months (n=2,018)



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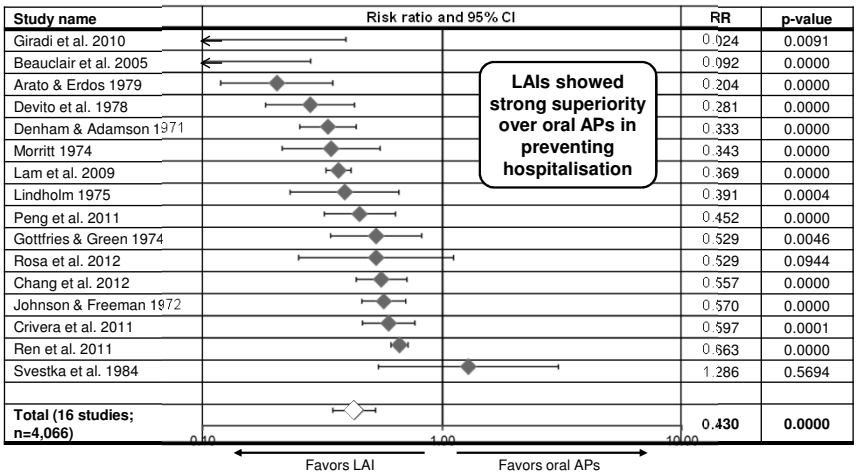
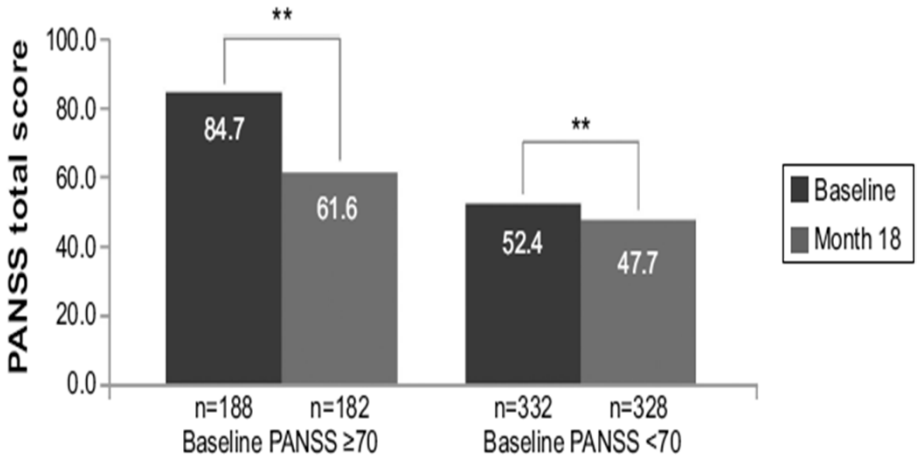
LAIs reduce risk of hospitalisation compared with oral antipsychotics



AP=antipsychotic; CI=confidence interval; LAI=long-acting injectable antipsychotic; RR=risk ratio

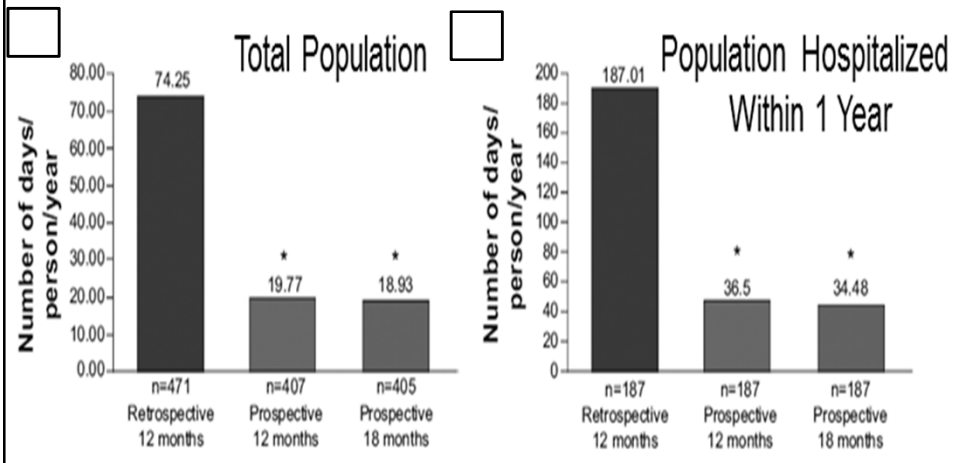
Kishimoto et al. J Clin Psychiatry 2013;74(10):957–965

PANSS Score Reduction with PALI-LAI in Recent-onset Schizophrenia (</=5 Years) Patients with Insufficient Response to Oral Antipsychotics (N=521)



Age, 28.7 years; 65.5% men, 92.5% Asian, illness duration: 0-<1: 36.4%, ≥4 years: 14.0%; prior AP use: 62%
58.0% completed the 18 months study Zhang F, et al. Neuropsychiatr Dis Treat. 2015 Mar 11;11:657-68.

Hospitalization Days Reduced with PALI-LAI in Recent-onset Schizophrenia (</=5 Years) Patients with Insufficient Response to Oral Antipsychotics (N=521)



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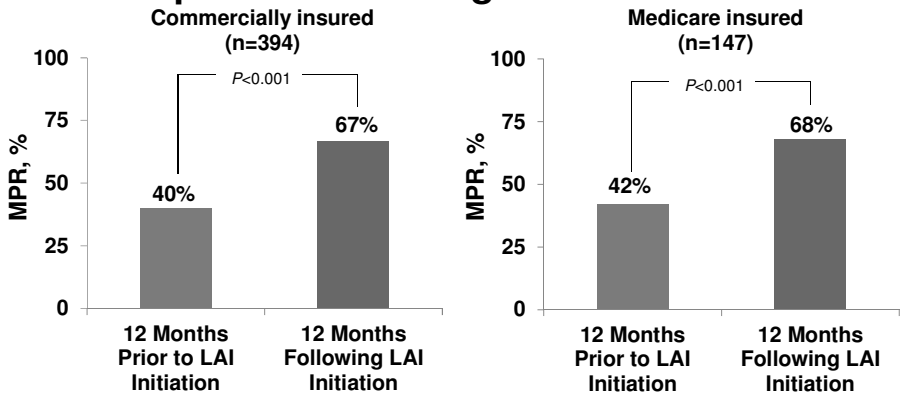
Medication Possession Ratio (MPR) Improved Following Initiation of LAIs

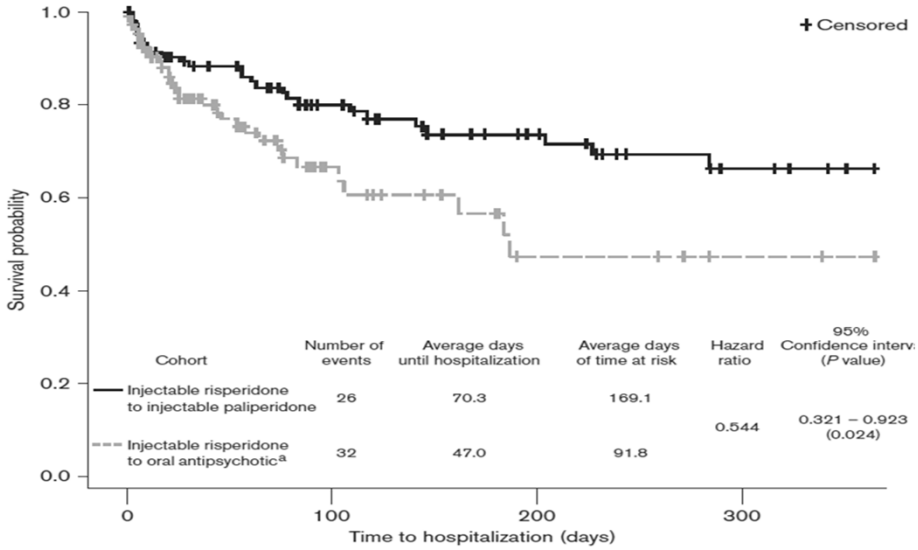


In an analysis of US databases, patients* who initiated LAI antipsychotics demonstrated an improvement in MPR

*Patients ≥3 years old were identified using an ICD-9 diagnosis of schizophrenic disorders (295.xx) on administrative claims, which includes schizophrenia, schizophreniform disorder, and schizoaffective disorder. ICD-9=*International Classification of Diseases, Ninth Revision*; LAI=long-acting injectable.

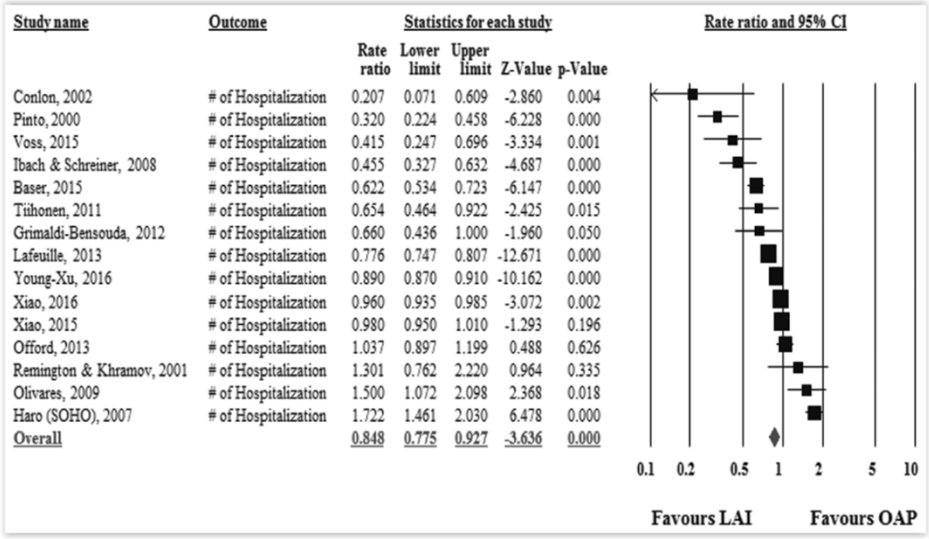
Offord S et al. *J Med Econ*. 2013;16(2):231-239.

Less Hospitalizations and Bed Days When Switching From RIS-LAI to PP-LAI Than from RIS-LAI to Oral Antipsychotics



Propensity Score Matched Survival Analysis Voss EA et al. Int Clin Psychopharmacol. 2015 May;30(3):151-7.

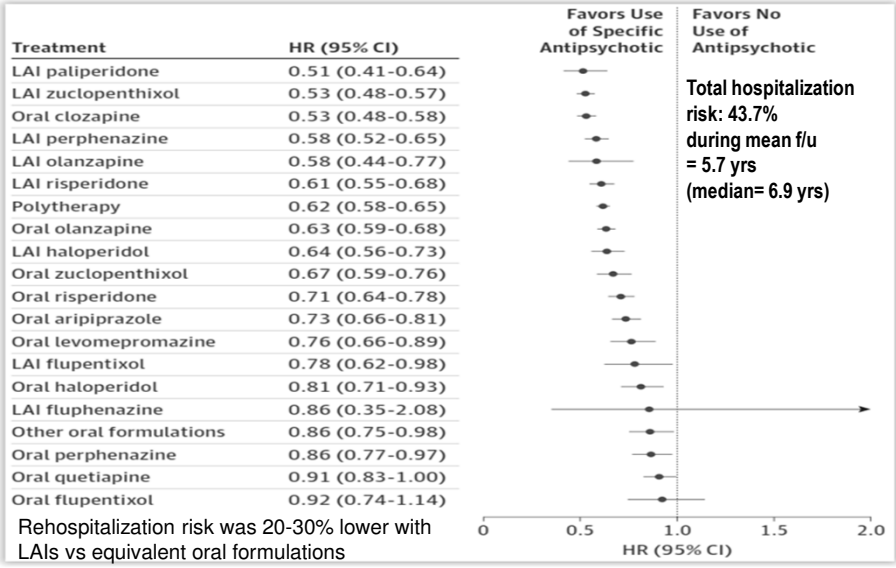
LATIs vs Oral Antipsychotics: Cohort Studies Number of Hospitalizations (N=14, 60,260 person-yrs)



Study name	Outcome	Rate ratio	Lower limit	Upper limit	Z-Value	p-Value
Conlon, 2002	# of Hospitalization	0.207	0.071	0.609	-2.860	0.004
Pinto, 2000	# of Hospitalization	0.320	0.224	0.458	-6.228	0.000
Voss, 2015	# of Hospitalization	0.415	0.247	0.696	-3.334	0.001
Ibach & Schreiner, 2008	# of Hospitalization	0.455	0.327	0.632	-4.687	0.000
Baser, 2015	# of Hospitalization	0.622	0.534	0.723	-6.147	0.000
Tiihonen, 2011	# of Hospitalization	0.654	0.464	0.922	-2.425	0.015
Grimaldi-Bensouda, 2012	# of Hospitalization	0.660	0.436	1.000	-1.960	0.050
Lafeuille, 2013	# of Hospitalization	0.776	0.747	0.807	-12.671	0.000
Young-Xu, 2016	# of Hospitalization	0.890	0.870	0.910	-10.162	0.000
Xiao, 2016	# of Hospitalization	0.960	0.935	0.985	-3.072	0.002
Xiao, 2015	# of Hospitalization	0.980	0.950	1.010	-1.293	0.196
Offord, 2013	# of Hospitalization	1.037	0.897	1.199	0.488	0.626
Remington & Khramov, 2001	# of Hospitalization	1.301	0.762	2.220	0.964	0.335
Olivares, 2009	# of Hospitalization	1.500	1.072	2.098	2.368	0.018
Haro (SOHO), 2007	# of Hospitalization	1.722	1.461	2.030	6.478	0.000
Overall		0.848	0.775	0.927	-3.636	0.000

41 trials (n=91,334; f/u=18.8±10.1 mo Kishimoto T, et al. Schizophr Bull 2017 Jul 27 [Epub ahead of print]

Adjusted HRs of Hospitalization with Specific AP Agents vs No AP (N=29,828 = 30,209 pt yrs)



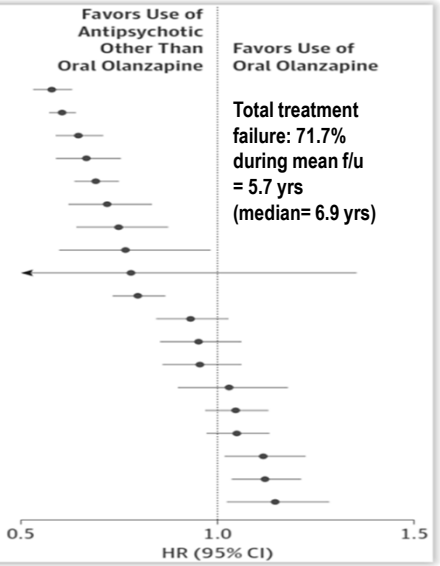
Treatment	HR (95% CI)
LAI paliperidone	0.51 (0.41-0.64)
LAI zuclopenthixol	0.53 (0.48-0.57)
Oral clozapine	0.53 (0.48-0.58)
LAI perphenazine	0.58 (0.52-0.65)
LAI olanzapine	0.58 (0.44-0.77)
LAI risperidone	0.61 (0.55-0.68)
Polytherapy	0.62 (0.58-0.65)
Oral olanzapine	0.63 (0.59-0.68)
LAI haloperidol	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)

Rehospitalization risk was 20-30% lower with LAIs vs equivalent oral formulations

HR= hazard ratio, median f/u: 6.9 yrs Tiihonen J et al. JAMA Psychiatry 2017 Jul 1;74(7):686-693.

Treatment Failure of Specific APs vs. oral OLA in Prevalent Population (N=29,828 = 30,209 pt yrs)

Treatment	HR (95% CI)
Oral clozapine *	0.58 (0.53-0.63)
Polytherapy	0.61 (0.57-0.64)
LAI perphenazine *	0.65 (0.59-0.71)
LAI haloperidol *	0.67 (0.59-0.75)
LAI zuclopenthixol*	0.69 (0.64-0.75)
LAI paliperidone *	0.72 (0.62-0.83)
LAI flupentixol *	0.75 (0.64-0.87)
LAI olanzapine	0.77 (0.60-0.98)
LAI fluphenazine	0.78 (0.45-1.35)
LAI risperidone *	0.80 (0.73-0.87)
Oral perphenazine	0.93 (0.84-1.03)
Oral zuclopenthixol	0.95 (0.85-1.06)
Oral haloperidol	0.96 (0.86-1.06)
Oral flupentixol	1.03 (0.90-1.18)
Oral quetiapine	1.05 (0.97-1.13)
Oral risperidone	1.05 (0.97-1.13)
Other oral formulations	1.12 (1.02-1.22)
Oral aripiprazole	1.12 (1.04-1.21)
Oral levomepromazine	1.15 (1.02-1.28)



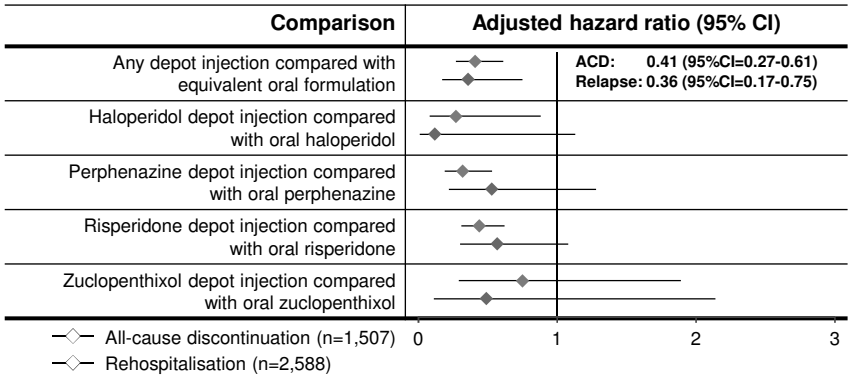
* p<0.05 vs oral OLA after Bonferroni correction

HR= hazard ratio, median f/u: 6.9 yrs Tiihonen J et al. JAMA Psychiatry 2017 Jul 1;74(7):686-693.

What is the Role of LAIs in the Treatment of Early Episode Patients?

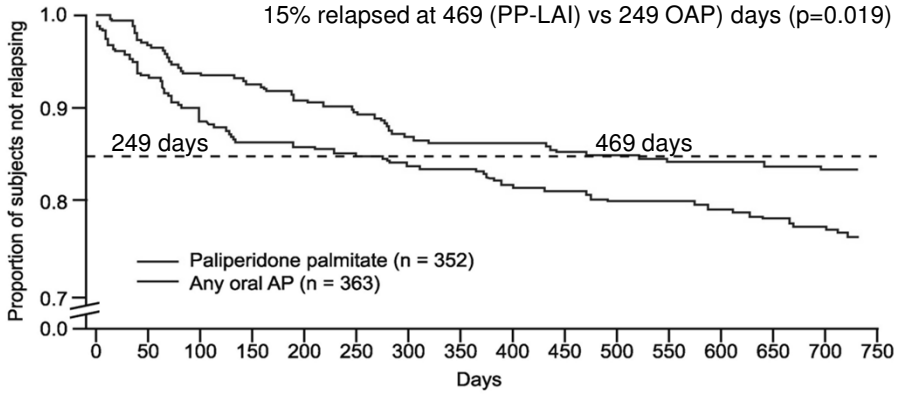
LAI antipsychotics significantly improve treatment outcomes in patients with schizophrenia

Risk of discontinuation or rehospitalization after a first hospitalization for schizophrenia, by antipsychotic treatment (n=2,588)



CI=confidence interval; LAI=long-acting injectable antipsychotic;
2000–2007; nationwide register study; follow-up after 1st admission for schizophrenia
Tiihonen et al. Am J Psychiatry 2011;168(6):603–609

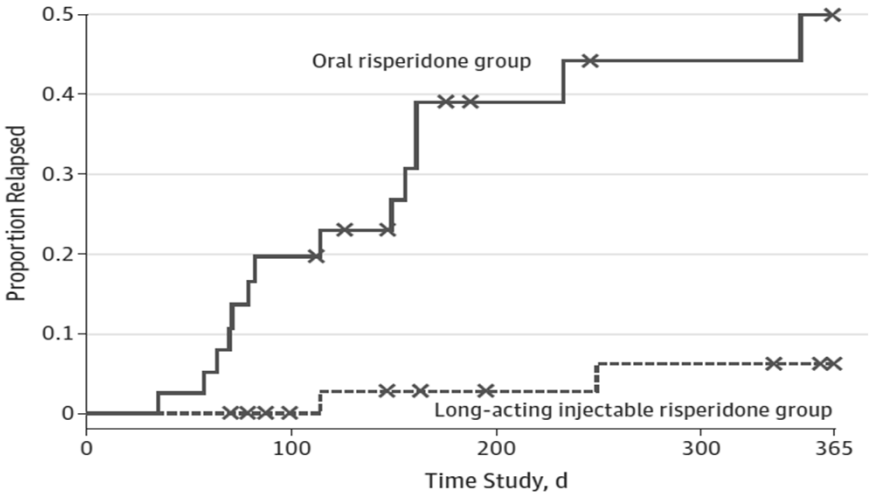
Significantly Longer Time to Relapse in Early Phase Schizophrenia Patients (1-5 Years) Randomized to PALI LAI vs Oral Antipsychotics



Subjects in treatment phase																
PP	352	326	306	292	278	272	260	256	252	244	237	233	230	225	221	0
Oral AP	363	323	297	280	265	258	246	242	230	227	216	212	207	201	198	0

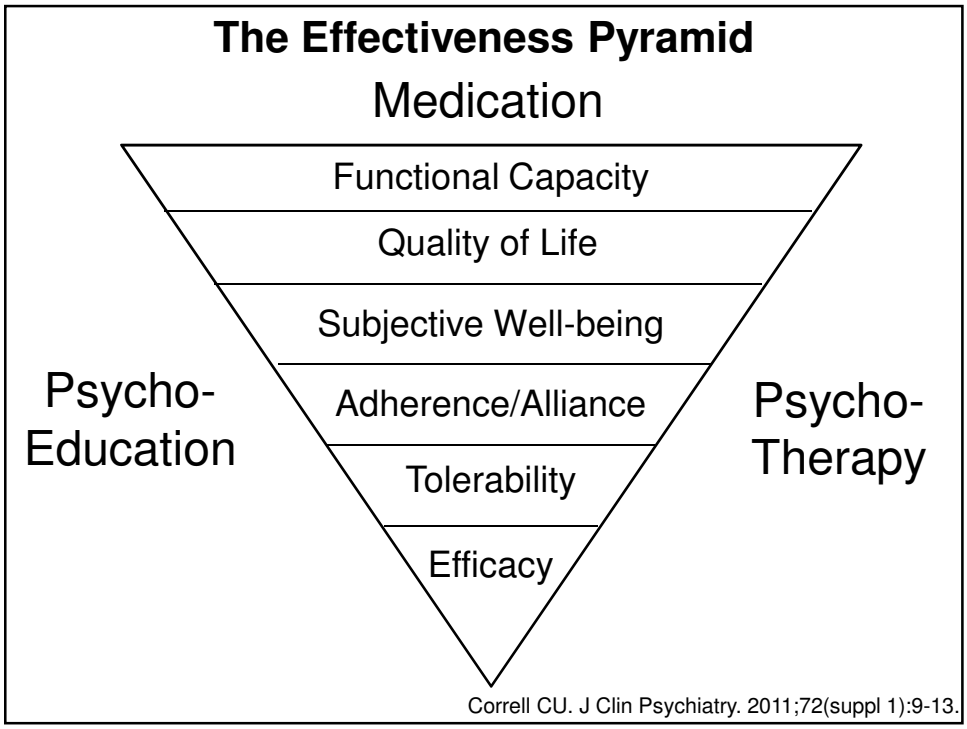
Relapse: PP-LAI=14.8% vs OAP=20.9% (p=0.03); 29.4% risk reduction, NNT=17
Schreiner A et al. Schizophr Res. 2015;169:393-399.

33% vs 5% Relapse in 86 FE Schizophrenia Patients Randomized to oral RIS vs. RISL LAI



Excellent adherence: RIS=33%, RIS LAI=95% Hospitalization: 5% vs 18.6% (p=0.05), NNT=8
Subotnik KL et al. JAMA Psychiatry. 2015 Aug;72(8):822-9.

Adverse Effects



Correll CU. J Clin Psychiatry. 2011;72(suppl 1):9-13.

Brain Volume Change in cc (=beta) Per Year of Relapse (A) Is 3 Times Larger than Per Year of 4 mg of HAL Equivalent Treatment (B)

A. **Brain Volume Decrease Per Year of Relapse**

Brain Volume Measure	β_2[a]	SE	Z	p
Cerebral				
Total	−1.55	0.61	−2.53	0.01
Gray matter	−0.78	0.53	−1.48	0.14
White matter	−0.95	0.54	−1.77	0.07
Surface CSF	0.68	0.40	1.71	0.09
Frontal lobe				
Total	−0.99	0.34	−2.91	0.004
Gray matter	−0.37	0.26	−1.42	0.16
White matter	−0.48	0.24	−2.02	0.04
Temporal lobe				
Total	−0.14	0.11	−1.21	0.23
Gray matter	−0.10	0.10	−1.00	0.32
White matter	−0.17	0.08	−2.12	0.03
Parietal lobe				
Total	−0.34	0.20	−1.74	0.08
Gray matter	−0.22	0.13	−1.70	0.09
White matter	−0.20	0.16	−1.22	0.22
Ventricle:brain ratio	0.01	0.01	0.75	0.45

B. **Brain Volume Decrease Per Year of AP Rx**

Brain Volume Measure	β_6[a]	SE	Z	p
Cerebral				
Total	−0.56	0.24	−2.34	0.01
Gray matter	−0.12	0.21	−0.58	0.56
White matter	−0.40	0.77	−1.51	0.13
Surface CSF	0.27	0.17	1.62	0.11
Frontal lobe				
Total	−0.28	0.12	−2.26	0.02
Gray matter	−0.12	0.12	−1.17	0.24
White matter	−0.20	0.12	−1.78	0.07
CSF	0.08	0.12	0.57	0.57
Temporal lobe				
Total	−0.12	0.06	−2.22	0.03
Gray matter	−0.6	0.04	−1.31	0.19
White matter	−0.02	0.04	−0.50	0.61
CSF	0.03	0.04	0.74	0.46
Parietal lobe				
Total	−0.12	0.08	−1.86	0.06
Gray matter	−0.02	0.05	0.44	0.66
White matter	−0.14	0.05	−2.54	0.01
CSF	0.13	0.06	2.16	0.03
Ventricle:brain ratio	0.008	0.003	2.44	0.01

N=202; 7 (5-18) years F/u, 659 scans; mean dose: 4 mg HAL eq Andreasen NC et al. Am J Psychiatry 2013;170:609-15.

Residual z-scores of Intracortical Frontal Lobe Myelin in FE SCZ Patients randomized to RIS Consta or RIS oral

			Baseline	Follow-up
	MED	N	Mean (SD)	Mean (SD)
Frontal ICM	RLAI	9	−.35 (1.26)	1.10 (2.49)
	RisO	13	.07 (1.44)	.38 (2.06)

		Within-group		Between-group		
MED	Change	t	p	F	p	d
RLAI	+1.53 (.98)	3.90	.005	3.13	.093	.81
RisO	+0.22 (1.60)	0.88	.39			

Bartzokis G. et al. Schizophr Research 2012. 140:122-8.

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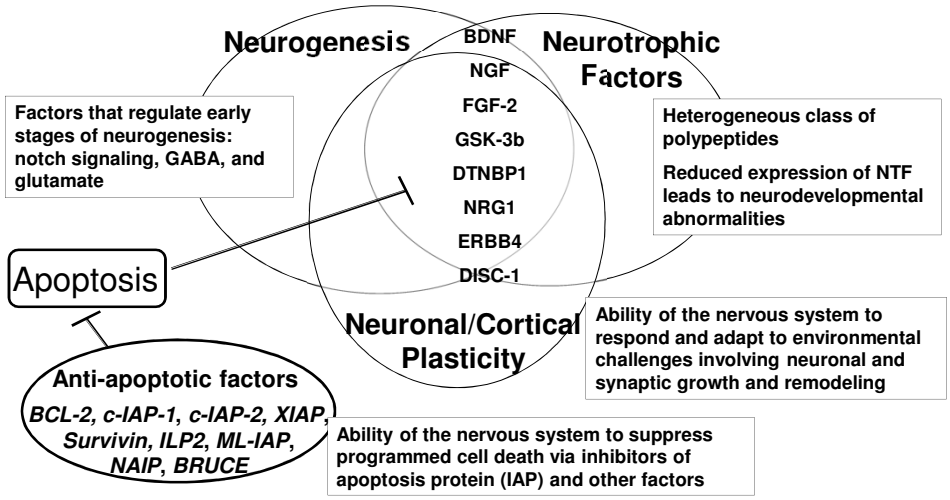
Neuroprotection: Growing Out of Psychosis?

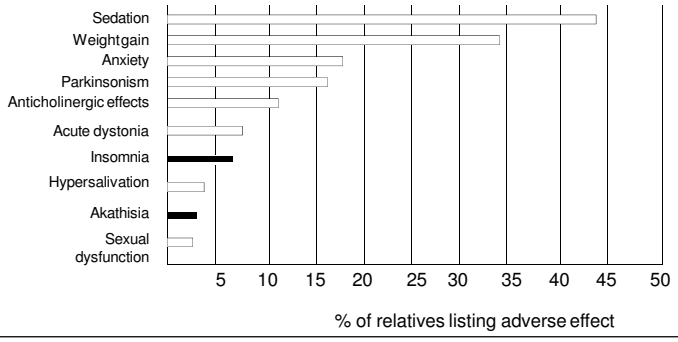


BCL-2= B cell leukemia 2 family proteins; BDNF = Brain-Derived Neurotrophic Factor; BRUCE= membrane-associated inhibitor of apoptosis protein; DTNBP-1 = Dystrobrevin Binding Protein 1; DISC-1 = Dysrupted in Schizophrenia 1; ERBB4 = neuregulin receptor; FGF-2 = Fibroblast Growth Factor; GSK-3b = Glycogen Synthase Kinase 3; IAP= inhibitor of apoptosis protein; ILP2= inhibitor of apoptosis like protein-2; MLAIP= melanoma inhibitor of apoptosis protein; NAIP= neuronal apoptosis inhibitory protein; NGF = Nerve Growth Factor; NGR-1= neuregulin; XIAP= x-linked inhibitor of apoptosis protein;

Le Strat Y, et al. *Curr Mol Med.* 2009; 9:506-518; Molteni R, et al. *Pharmacol Ther.* 2009;124:74-85; Calabrese F, et al. *Psychoneuroendocrinology.* doi:10.1016/j.psyneuen.2009.05.014. 2009; Eisch AJ, et al. *J Neurosci.* 2008;28:11785-11791.

Adverse Effects Considered by Patients' Relatives to Have Most Negative Effects on Quality of Life

Written survey of relatives of patients with schizophrenia, n=320



Angermeyer MC et al. *Psychiat Prax* 1999; 26: 171-174.

Adverse Events Considered by Patients to Have Most Negative Effect on Quality of Life

UNITE survey was an internet-based multinational survey with 1,300 respondents with bipolar disorder from 11 countries

Patients rated metabolic consequences of medication to contribute to morbidity, low quality of life and low satisfaction with care

Weight gain

Somnolence/insomnia

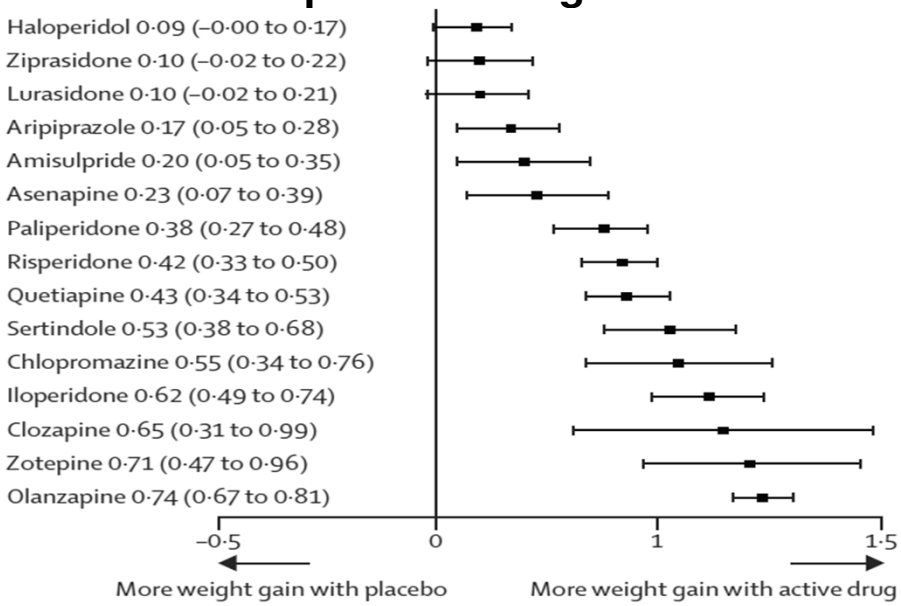
Concentration difficulties

Memory loss

Disorganised thoughts

McIntyre RS. *J Clin Psychiatry* 2009; 70(suppl 3): S5-S11.

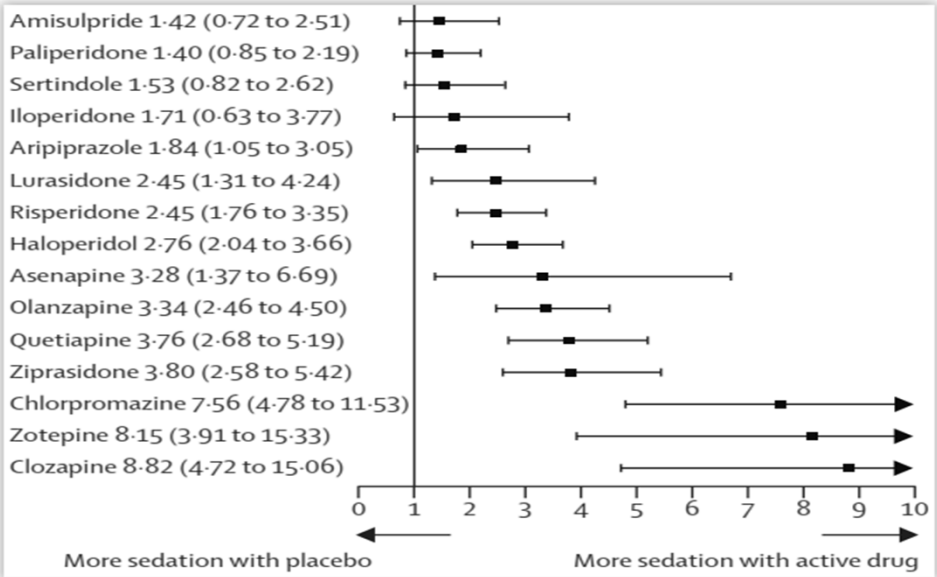
Acute Treatment Network Metaanalysis in Schizophrenia: Weight Gain



Total Efficacy: SMD +/- 95% CIs

Leucht S. et al. Lancet. 2013 Sep 14;382(9896):951-62.

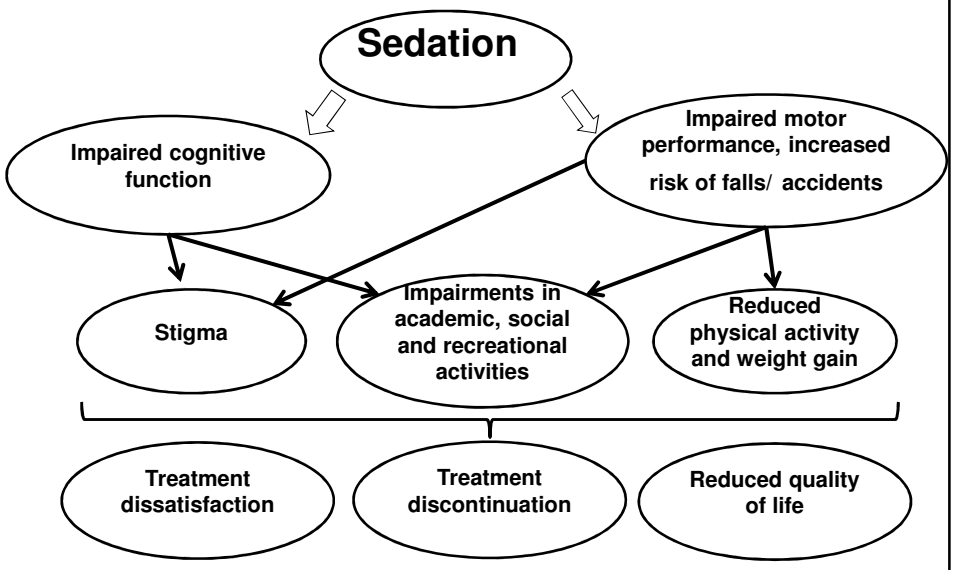
Acute Treatment Network Metaanalysis in Schizophrenia: Sedation



SMD +/- 95% CIs

Leucht S. et al. Lancet. 2013 Sep 14;382(9896):951-62.

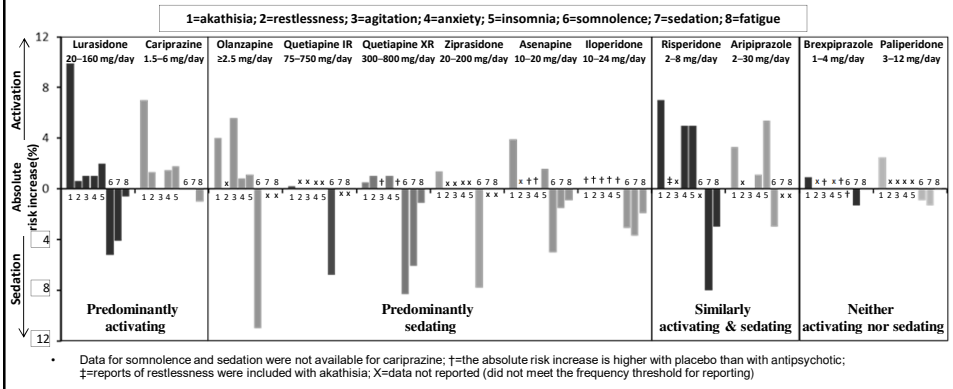
Potential Consequences of Sedation



Adapted from Kane et al. *J Clin Psychiatry* 2008;69(Suppl 1):18–31

Activating and Sedating Adverse Effects Vary Among Antipsychotics

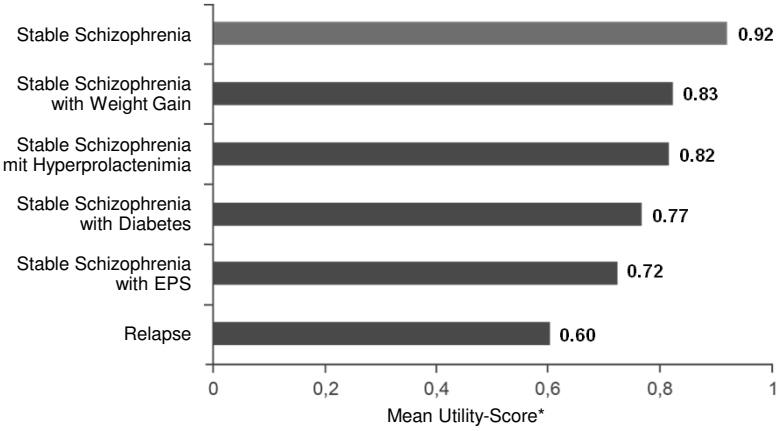
Antipsychotic-associated activating and sedating adverse events, as observed in short-term acute placebo-controlled clinical trials for first-line oral second generation antipsychotics approved for the treatment of schizophrenia



- Data for somnolence and sedation were not available for cariprazine; †=the absolute risk increase is higher with placebo than with antipsychotic; ‡=reports of restlessness were included with akathisia; X=data not reported (did not meet the frequency threshold for reporting)

Citrome. J Clin Psychopharmacol 2017;37(2):138–147

Relapse and Adverse Efffects Reduce Quality of Life in Patients with Schizophrenia



*The relevance of the different health states was assessed using a Time-Tradeoff instrument. Higher scores reflect better utility for the patient.
EPS = Extrapyramidal side effects

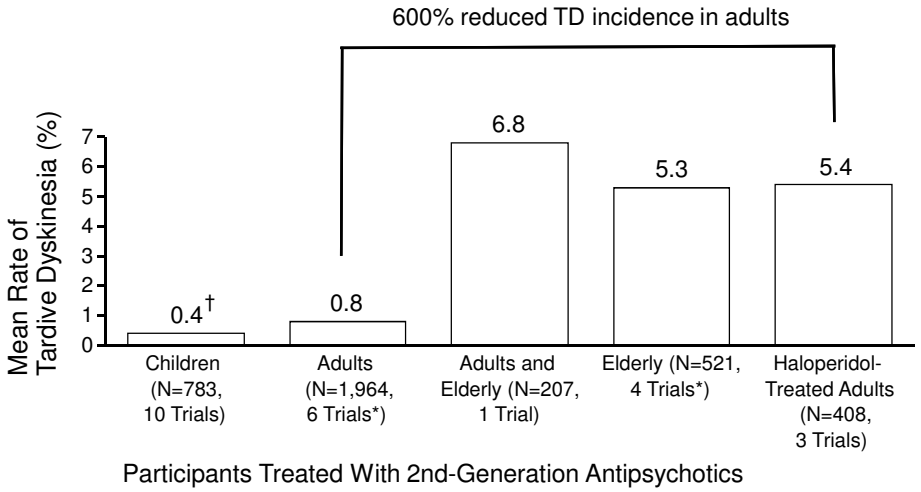
Briggs A et al., Health Qual Life Outcomes 2008; 6:105

TD Prevalence Meta-Analysis: Overview

- 41 studies: n=11,493, mean age=42.8 years, male=66.4%, schizophrenia-spectrum disorders=77.1%
- The global mean TD prevalence was 25.3% (95%CI=22.7-28.1%).
- Rates were lower with current SGA treatment (20.7%; 95%CI=16.6-25.4%, N=5,103) vs. current FGA treatment (30.0%; 95%CI=26.4-33.8%, N=5,062; p=0.002).
- Lower TD prevalence of SGA relative to FGA was also confirmed in the subgroup of studies assessing and directly comparing ≥2 antipsychotic classes/combinations:
  - SGAs vs. FGAs (risk ratio=0.80; 95%CI=0.67-0.95, p=0.011);
  - SGA+FGA vs FGA. (risk ratio=0.80, 95%CI=0.71-0.90, p<0.001).
- TD prevalence with SGAs was especially low in the 4 studies reporting on patients without prior FGA treatment: 7.2%

Carbon M et al. J Clin Psychiatry. J Clin Psychiatry. 2017 Mar;78(3):e264-e278.

Mean Weighted 1-Year Incidence Rates of TD



*1 study reported separate rates for TD in adults and in the elderly; Correll CU et al. (2004), Am J Psychiatry 161(3):414; †Correll CU, Kane JM (2004), J Child Adolesc Psychiatry, 17(5): 647-65.

TD in the Elderly: FGAs

- The cumulative rates TD after cumulative antipsychotic treatment in a group of 261 neuroleptic-naive patients aged 55 or above were:
  - After 1 year = 25%
  - After 2 years = 34%,
  - After 3 years = 53%
- A greater risk of TD was associated with history of ECT treatment, higher mean daily and cumulative antipsychotic doses, and presence of EPS early in treatment
- TD rates for patients beginning treatment with conventional antipsychotics in their fifth decade or later were three to five times what has been found for younger patients, despite treatment with lower doses

Woerner M et al. *Am J Psychiatry.* 1998 Nov;155(11):1521-8.

TD in the Elderly: Cumulative TD with Risperidone and Olanzapine

Group	n	1 year Rate (%)	1 year 95% CI	2 year Rate (%)	2 year 95% CI
Total	207	5.7	1.5, 10.0	8.2	2.9, 13.4
All risperidone	159	5.3	0.7, 9.9	7.2	1.4, 12.9
All olanzapine	48	6.7	0.0, 15.6	11.1	0.0, 23
'Pure' risperidone	159	4.7	0.0, 9.5	7.1	0.6, 13.7
'Pure' olanzapine	48	4.0	0.0, 11.8	10.4	0.0, 25

Woerner M et al. Neuropsychopharmacology. 2011 Jul;36(8):1738-46.

Comparative Data - Conventional Antipsychotics[1] NNH and LHH

- Benefits (NNT) were similar between paliperidone palmitate and fluphenazine decanoate; however, certain measures of harm favored paliperidone palmitate
- NNH favored paliperidone palmitate over fluphenazine decanoate for anticholinergic medication use (30 vs. 5), tardive dyskinesia (infinity vs. 7), emergence of positive AIMS score (-32 vs. 13)

Comparison of interest	NNT	NNH
Benefit: Prevention of Relapse		
Paliperidone LAI vs Placebo[2]	2	Anticholinergic medication use: 30.0 Tardive dyskinesia: infinity Emergent positive AIMS score: -32
Fluphenazine LAI vs Placebo[3-5]	2[3] 3[4] 3[5]	Anticholinergic medication use: 5.0 Tardive dyskinesia: 7.0 Emergent positive AIMS score: 13.0

[1]Gopal S, et al. *Neuropsychiatr Dis Treat* 2011;93-101;[2]Hough D, et al. *Schizophr Res* 2010;116:107-117. [3]Hirsch SR, et al. *Br Med J* 1973;1(5854):633-637. [4]Jolley AG, et al. *BMJ* 1990;301(6756):837-842. [5]Odejide OA, et al. *J Clin Psychiatry* 1982;43(5):195-196. [6]Pandina GJ, et al. *J Clin Psychopharmacol* 2010;30:235-244.

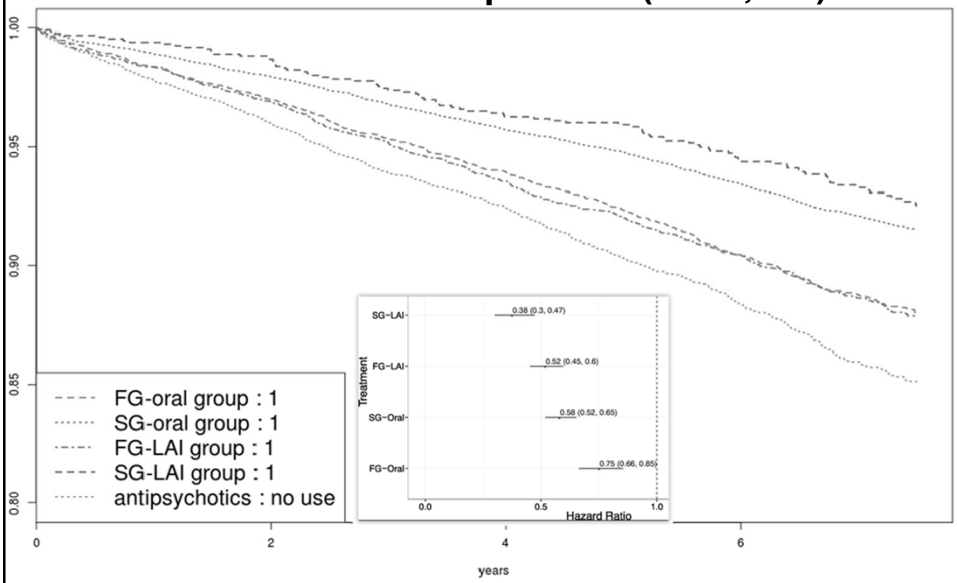
Adverse Effects with LAI vs Same Oral Antipsychotics (N=16, n=4,902)

No Difference in Frequency of At Least OneAdverse Effect

- **Out of all 119 adverse events, LAIs and OAPs did not differ significantly regarding 115 (96.6%).**
- **LAIs were associated with more akinesia, low-density lipoprotein cholesterol change and anxiety.**
- **LAIs were associated with significantly lower prolactin change.**

Misawa F et al. *Schizophr Res* 2016; 176(2-3): 220-30.

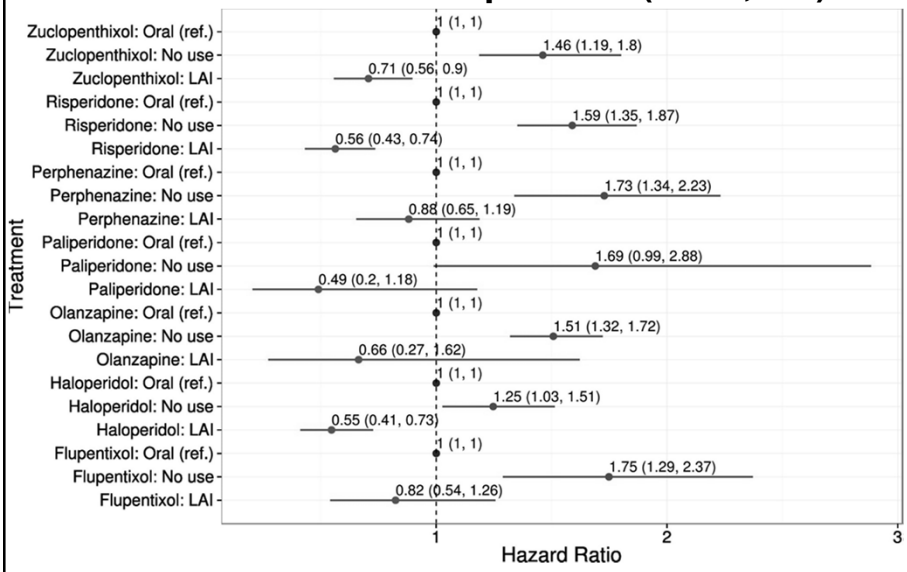
Mortality of oral and LAI SGAs and FGAs vs. no AP Use in Prevalent Population (N=29,823)



HR= hazard ratio, median f/u: 5.7 yr Taipale H et al. Schizophr Res 2017 Dec 20. [Epub ahead of print]

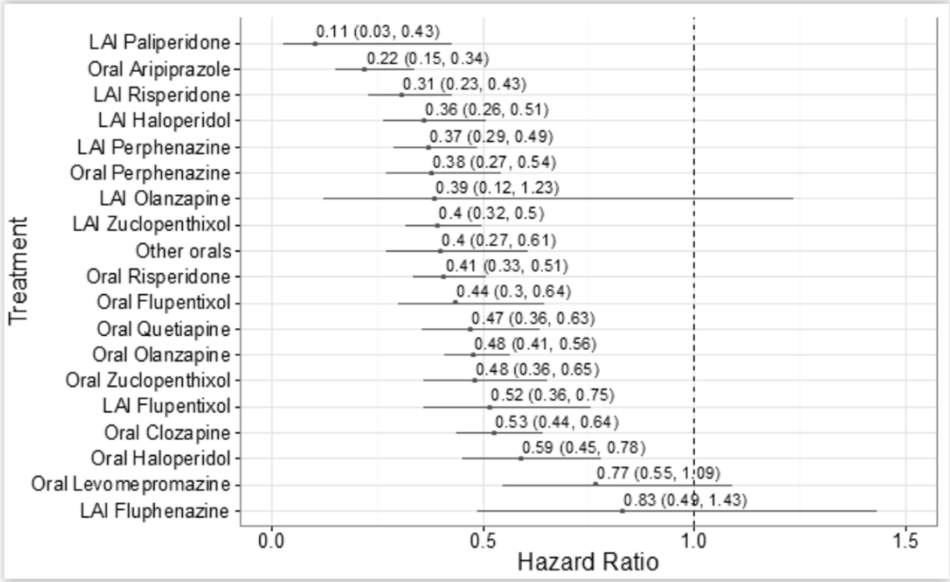
AP: antipsychotic

Mortality of oral and LAI SGAs and FGAs vs. no AP Use in Prevalent Population (N=29,823)



HR= hazard ratio, median f/u: 5.7 yr Taipale H et al. Schizophr Res 2017 Dec 20. [Epub ahead of print]
AP: antipsychotic

Mortality of Specific APs vs. no AP Use in Prevalent Population (N=29,823)

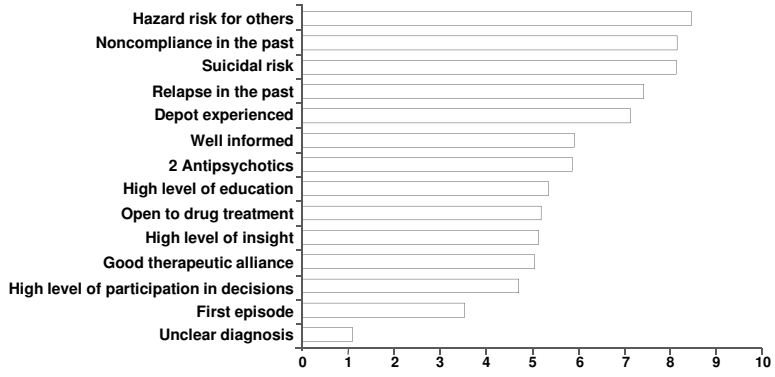


HR= hazard ratio, median f/u: 5.7 yr Taipale H et al. Schizophr Res 2017 Dec 20. [Epub ahead of print]
AP: antipsychotic

Offering LAIs

Several Patient Attributes Were Cited as Influencing Qualification for LAI Antipsychotic Treatment

Mean rating of the attributes potentially influencing the qualification for LAI treatment

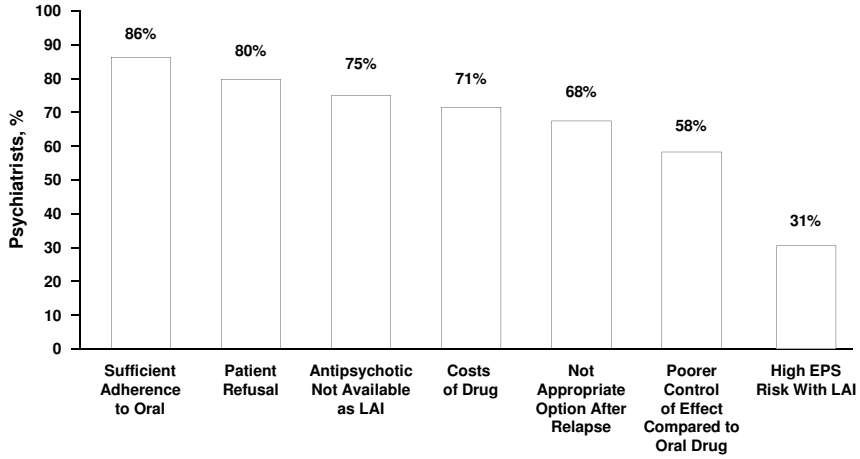


The primary patient characteristic influencing the psychiatrist's decision to initiate LAI antipsychotic therapy was "hazard risk for others"

0=not qualifying for LAI treatment, while 10=highly qualifying for LAI treatment.
LAI=long-acting injectable.

Heres S et al. *Prog Neuropsychopharmacol Biol Psychiatry.* 2008;32(8):1987-1993.

Psychiatrists Cite Multiple Reasons for Not Prescribing LAI Atypical Antipsychotics



EPS=extrapyramidal symptom; LAI=long-acting injectable.

Heres S et al. *J Clin Psychiatry*. 2006;67(12):1948-1953.

6

Goal Elicitation and Goal Setting

"The new screen saver was created by a motivation expert. It's a slide show of former employees who were fired for poor performance."

Style

Whose Carrot is it Anyway?

Presentation Matters….

- Discourse analysis of 33 recorded conversations in which a psychiatrist offered a long-acting treatment antipsychotic to a patient with schizophrenia.
- Psychiatrists focused on the modality (“injection”, “shot”: 91%), rarely on the benefits (9%).
- Only 11 of 33 recommendations (33%) were accepted during the initial discussion.
- On the post-visit interview – involving probing of patients’ feelings about medications - 27 of 28 patients (96%) who declined the initial offer said they would be willing to try an LAI.

Weiden PJ et al. J Clin Psychiatry 2015 Jun;76(6):684-90.

Goal Elicitation and Goal Setting

“What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?”

Conclusions

- Functional outcomes are extremely important
- Response and remission are only the beginning of the read to recovery
- However, symptom stability is needed for
  - psychosocial interventions to be delivered for long enough and with sufficient client-focused intensity
  - patients not to suffer biological, psychological and social adverse effects of relapse that diminish future chances for recovery
- Maintenance treatment and relapse prevention are the building block for person-centered, functionality-oriented outcomes
- Adequate choice of antipsychotics and, ideally, earlier use of LAIs that are well tolerated and promote recovery, are relevant

LAI = long-acting antipsychotic

Summary

- In the treatment of schizophrenia, acute and long-term goals must be linked early on
- Efficacy differences are harder to predict and much smaller than adverse effect differences
- Maintenance therapy and relapse prevention are pivotal goals in the management of schizophrenia
- Relapses are serious events that most often are related to non-adherence
- LAI-antipsychotics are a highly valuable, yet still underutilised treatment option
- Earlier use of LAI antipsychotics is hoped to benefit the overall disease course and outcome
- The risk-benefit ratio of treatments must be considered when choosing among available options

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