Thinking Long-term From the Beginning to Optimize Outcomes in Schizophrenia

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Disclosures: Christoph U. Correll

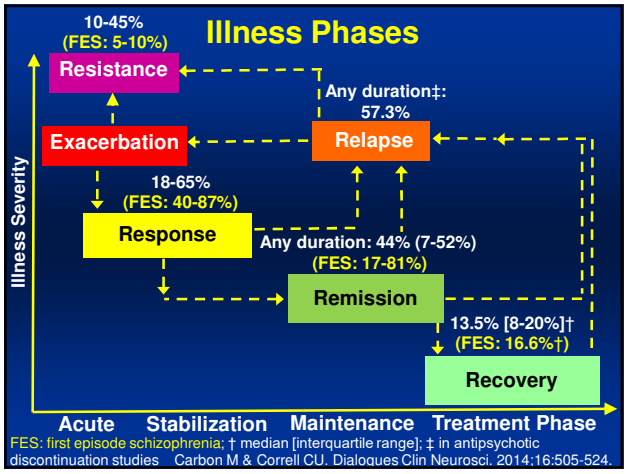
I have an interest in relation with one or more organizations that could be perceived as a possible conflict of interest in the context of this presentation. The relationships are summarized below:

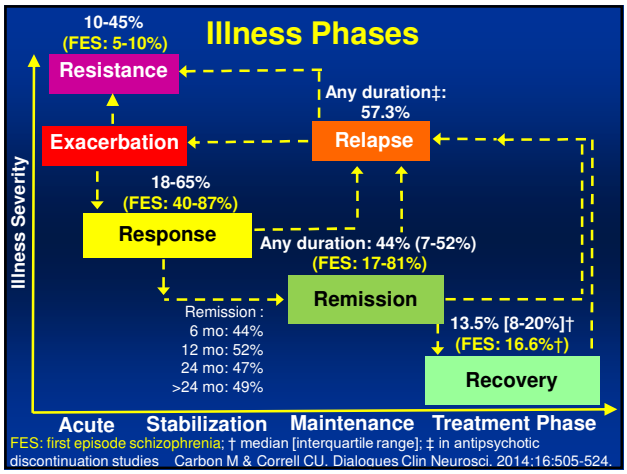
Interest	Name of organization
Grants	National Institute of Mental Health (NIMH), Patient Centered Outcomes Research Institute (PCORI), Takeda, Thrasher Foundation
Shares	No share holdings in pharmaceutical companies
Paid positions, honoraria and advisory boards	Alkermes, Bristol-Myers Squibb, Forum,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

Overview

- Efficacy
  - –First Episode Patients
  - –Chronic Patients
  - –Maintenance Treatment
- Adverse Effects
- Conclusions

Efficacy


Illness Phases
10-45%
(FES: 5-10%)
Resistance
Any duration‡:
57.3%
Exacerbation
Relapse
18-65%
(FES: 40-87%)
Response
Any duration: 44% (7-52%)
(FES: 17-81%)
Remission
13.5% [8-20%]†
(FES: 16.6%†)
Recovery
Illness Severity
Acute
Stabilization
Maintenance
Treatment Phase
FES: first episode schizophrenia; † median [interquartile range]; ‡ in antipsychotic discontinuation studies
Carbon M & Correll CU. Dialogues Clin Neurosci. 2014;16:505-524.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Resistance
Any duration‡:
57.3%
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18-65%
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Response
Any duration: 44% (7-52%)
(FES: 17-81%)
Remission
Remission :
6 mo: 44%
12 mo: 52%
24 mo: 47%
>24 mo: 49%
13.5% [8-20%]†
(FES: 16.6%†)
Recovery
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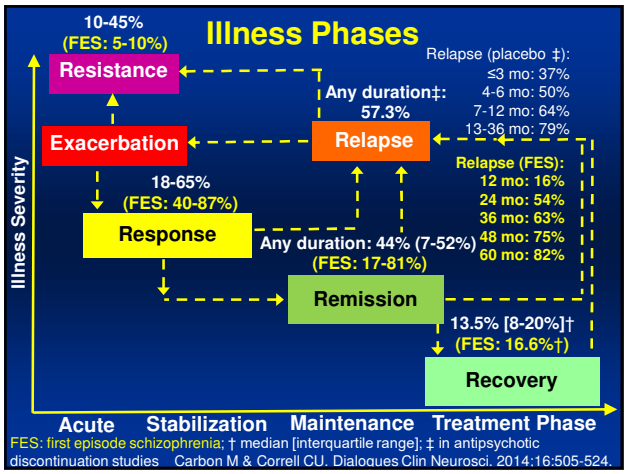
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Resistance
Exacerbation
18-65%
(FES: 40-87%)
Response
Any duration‡:
57.3%
Relapse
Relapse (placebo ‡):
≤3 mo: 37%
4-6 mo: 50%
7-12 mo: 64%
13-36 mo: 79%
Relapse (FES):
12 mo: 16%
24 mo: 54%
36 mo: 63%
48 mo: 75%
60 mo: 82%
Any duration: 44% (7-52%)
(FES: 17-81%)
Remission
13.5% [8-20%]†
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Recovery
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Acute
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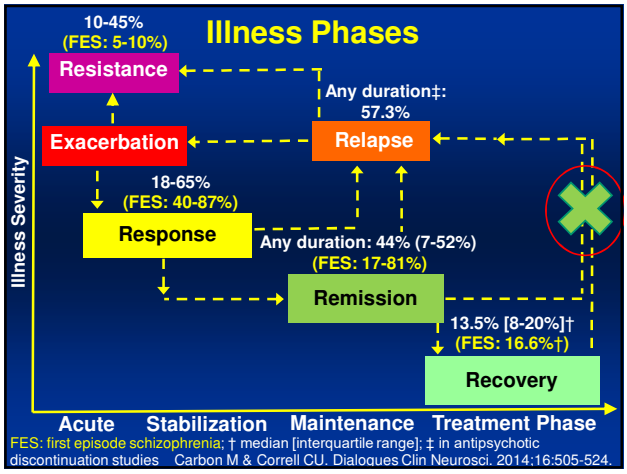
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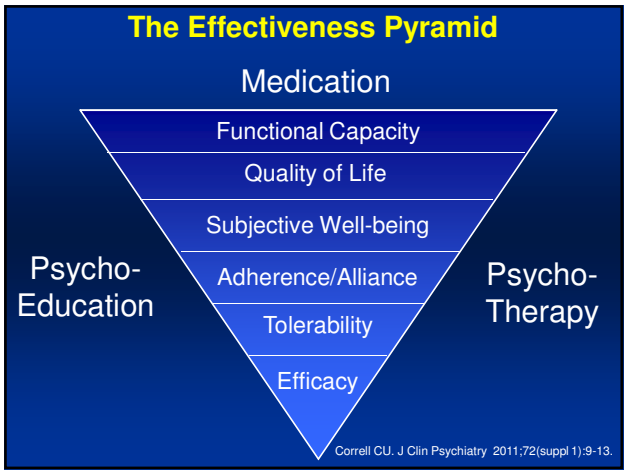
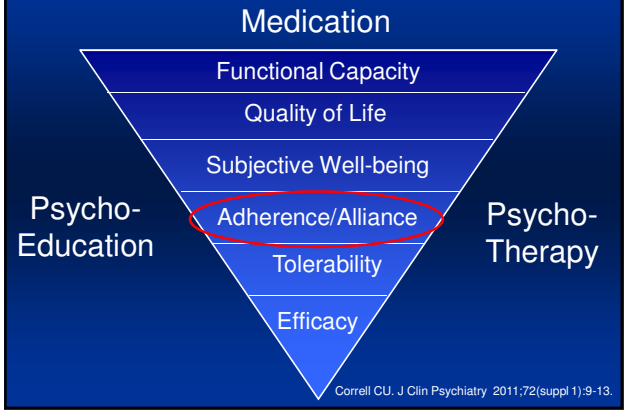

The Effectiveness Pyramid
Medication
Functional Capacity
Quality of Life
Subjective Well-being
Adherence/Alliance
Tolerability
Efficacy
Psycho-Education
Psycho-Therapy
Correll CU. J Clin Psychiatry 2011;72(suppl 1):9-13.

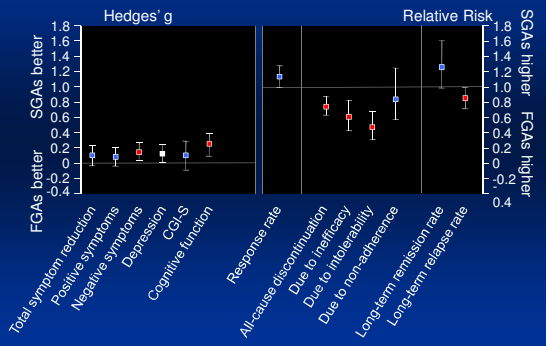
The Effectiveness Pyramid



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

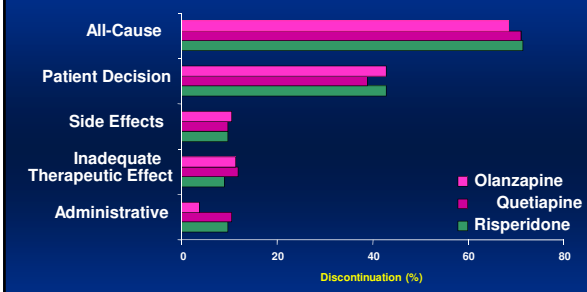
First Episode

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



Zhang JP et al. Int J Neuropsychopharm. 2013 Jul;16(6):1205-18.

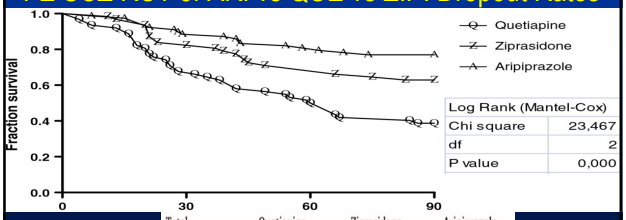
CAFE Study: All-Cause Treatment Discontinuation



For each category above, the comparison of quetiapine vs olanzapine and quetiapine vs risperidone met the *a priori* test of noninferiority (20%) at $P<0.05$

McEvoy J et al. Am J Psychiatry 2007;164:1050-60.

FE SCZ RCT of ARI vs QUE vs ZIP: Dropout Rates



	Total (N = 202)		Quetiapine (N = 62)		Ziprasidone (N = 62)		Aripiprazole (N = 78)			
	N	%	N	%	N	%	N	%	χ^2 (df = 2)	p
Discontinuation for any cause	79	39.1	38	61.3	23	37.1	18	23.1	21.334	0.000
Discontinuation: insufficient efficacy	33	16.3	21	33.9	6	9.7	6	7.7	20.223	0.000
Discontinuation: side effects	20	9.9	7	11.3	8	12.9	5	6.4	1.826	0.401
Discontinuation: non-compliance	2	1.0	1	1.6	0	0.0	1	1.3	0.933	0.627
Discontinuation: drop-out	24	11.9	9	14.5	9	14.5	6	7.7	2.130	0.345

Crespo-Facorro B et al. Schizophr Research 2013 Jul;147(2-3):375-82.

Schizophrenia Bulletin
doi:10.1093/SCHBUL/SBV125

A Randomized Comparison of Aripiprazole and Risperidone for the Acute Treatment of First-Episode Schizophrenia and Related Disorders: 3-Month Outcomes

Delbert G. Robinson[*,1-4], Juan A. Gallego[1-3], Majnu John[1,2,5], Georgios Petrides[1-4], Youssef Hassoun[2,3], Jian-Ping Zhang[1-3], Leonardo Lopez[2,3], Raphael J. Braga[2,3], Serge M. Sevy[6], Jean Addington[7], Charles H. Kellner[8], Mauricio Tohen[9], Melissa Naraine[2], Natasha Bennett[2], Jessica Greenberg[2], Todd Lencz[1-4], Christoph U. Correll[1-4,10], John M. Kane[1-4,10,11], and Anil K. Malhotra[1-4,11]

Research findings are particularly important for medication choice for first-episode patients as individual prior medication response to guide treatment decisions is unavailable. We describe the first large-scale double-masked randomized comparison with first-episode patients of aripiprazole and risperidone, 2 commonly used first-episode treatment agents. One hundred ninety-eight participants aged 15–40 years with schizophrenia, schizophreniform disorder, schizoaffective disorder or psychotic disorder Not Otherwise Specified, and who had been treated in their lifetime with antipsychotics for 2 weeks or less were randomly assigned to double-masked aripiprazole (5–30 mg/d) or risperidone (1–6 mg/d) and followed for 12 weeks. Positive symptom response rates did not differ (62.8% vs 56.8%) nor did time to response. Aripiprazole-treated participants had better negative symptom outcomes but experienced more akathisia. Body mass index change did not differ between treatments but advantages were found for aripiprazole treatment for total and low-density lipoprotein cholesterol, fasting glucose, and prolactin levels. Post hoc analyses suggested advantages for aripiprazole on depressed mood. Overall, if the potential for akathisia is a concern, low-dose risperidone as used in this trial maybe a preferred choice over aripiprazole. Otherwise, aripiprazole would be the preferred choice over risperidone in most situations based upon metabolic outcome advantages and some symptom advantages within the context of similar positive symptom response between medications.

1st Episode Schizophrenia: Key Points

- First episode patients are generally more treatment responsive
- They require lower doses (approx. 50%)
- 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

Multi-episode / Chronic

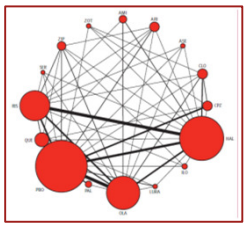
Multiple treatments meta-analysis[1]

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 RCTs
- Acute schizophrenia
- 43,049 participants
- Mean illness duration: 12.4 yrs
- Mean age: 38.4 yrs

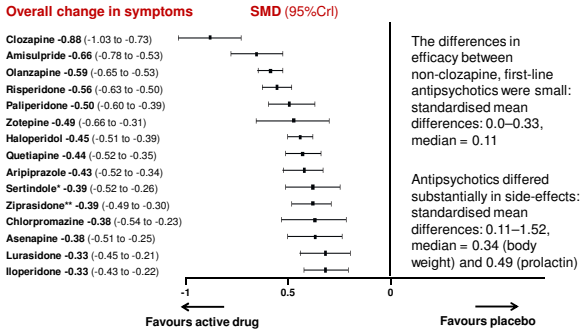


Network of comparisons for efficacy

RCT: randomised control trials

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

Efficacy of antipsychotics vs. placebo



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)

* Only available on named patient basis in UK ** Not licensed in the UK

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

Magnitude PANSS Total Change on Placebo Over Time in Trials of Acute SCZ

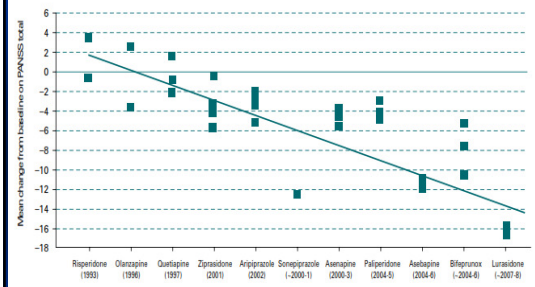
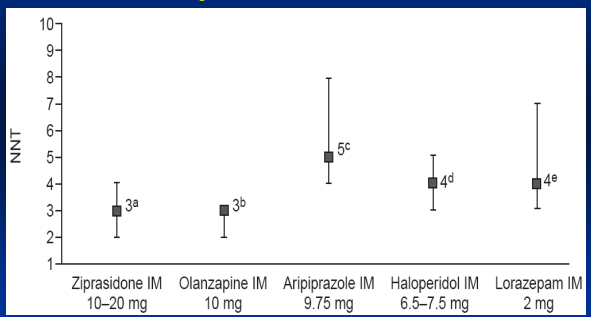


Fig. 2. Placebo effect in acute schizophrenia trials over time. The mean change from baseline in total Positive and Negative Syndrome Scale (PANSS) scores for subjects receiving placebo across randomized, double-blind, placebo-controlled, clinical trials has increased in the direction of greater improvements that is correlated to the year that the studies were conducted. (Adapted from Kemp *et al*. 2008.)

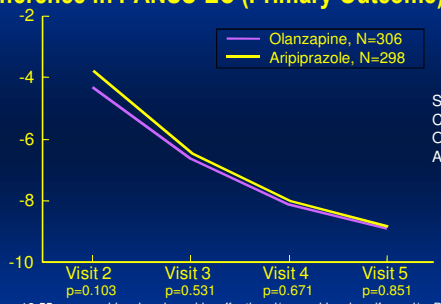
Alphs L et al. Int J Neuropsychopharmacol. 2012 Aug;15(7):1003-14

Short Acting i.m. Antipsychotics for Acute Agitation: NNTs for Study-defined Response at 2 Hours



Citrome, L. J Clin Psychiatry 2007; 68(12):1876-85

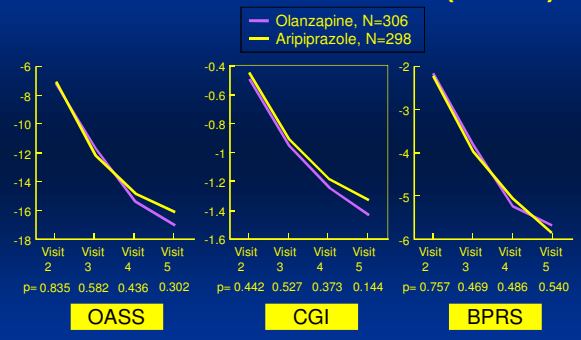
5-Day Randomized Trial of Olanzapine vs. Aripiprazole in Acutely Ill Schizophrenia Patients with Agitation: No Difference in PANSS-EC (Primary Outcome) (N=604)



Study Completion:
OLA: 76.3%
ARI: 79.5%

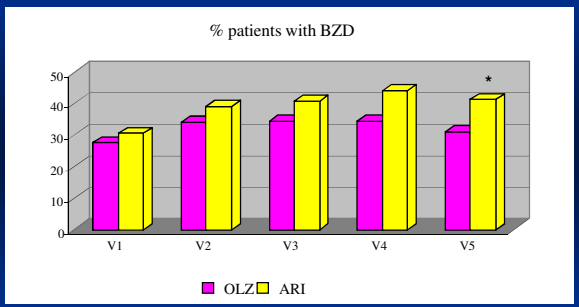
Inclusion: Age: 18-55 years, schizophrenia, schizoaffective d/o or schizophreniform d/o; PANSS-EC score of ≥20 (1-7 scale) and rated >4 (1-7 scale) on at least 2 of the BPRS Positive subscale items, minimum hospitalization of at > 5 d;Baseline Mean total PANSS-EC score: Olanzapine = 21.63 Aripiprazole= 21.43
Kinon B et al., J Clin Psychopharmacol. 2008 Dec;28(6):601-7.

Change in OASS, CGI-Severity and BPRS Positive Scores (N=604)



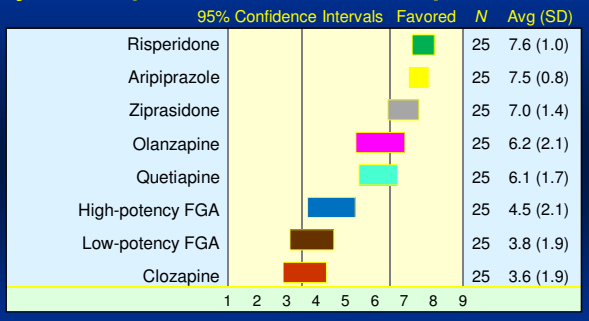
OASS= Overt Agitation Severity Scale; CGI= Clinical Global Impressions; BPRS= Brief Psychiatric Rating Scale
Kinon B et al., J Clin Psychopharmacol. 2008 Dec;28(6):601-7.

Concomitant Benzodiazepine Use (N=604)



* p=0.033, all other time points: ns
Baseline Mean total PANSS-EC score: Olanzapine = 21.63 Aripiprazole= 21.43
Kinon B et al., J Clin Psychopharmacol. 2008 Dec;28(6):601-7.

Expert Consensus on the Treatment of the Acute Psychotic Episode as Part of Schizophrenia

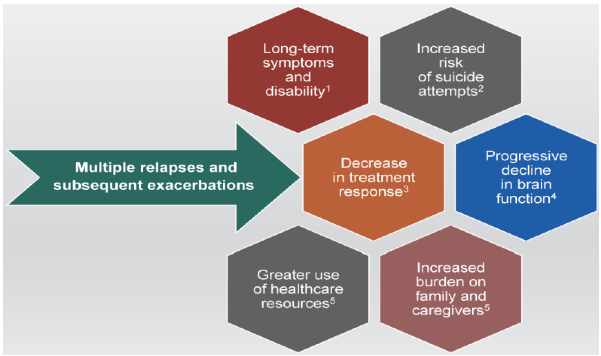


9= extremely appropriate: first strategy of choice
7-8= usually appropriate: a 1st line strategy you would often use
4-6= equivocal: 2nd line strategy you would sometimes use, eg, pt/fx preference, 1st line not effective/available/suitable
2-3= usually inappropriate: strategy you would rarely use;
1 = extremely inappropriate: strategy you would never use

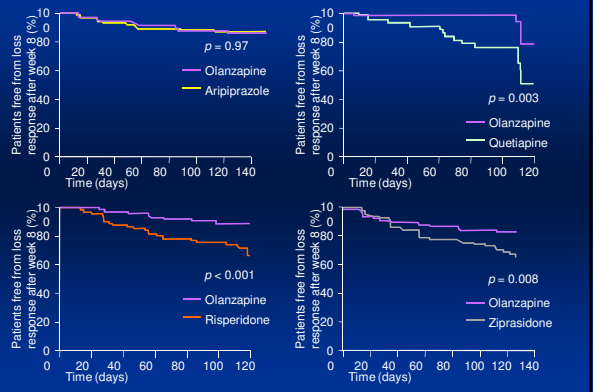
Weiden PJ et al. J Clin Psychiatry. 2007;68 Suppl 7:1-48

Maintenance

What is the Importance of Relapse Prevention?

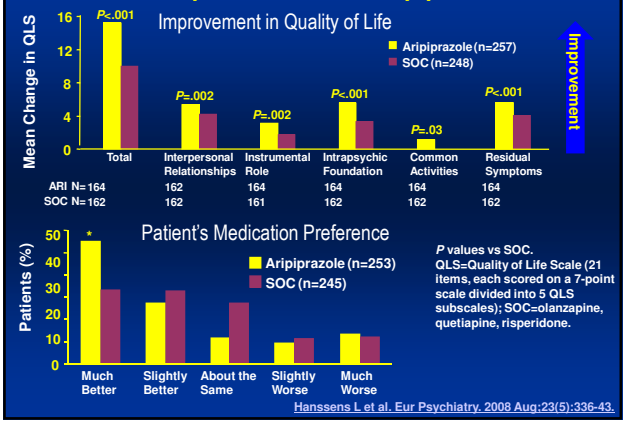


Maintenance of Response with Atypical Antipsychotics



Stauffer V *et al. BMC Psychiatry* 2009;9:13-24.

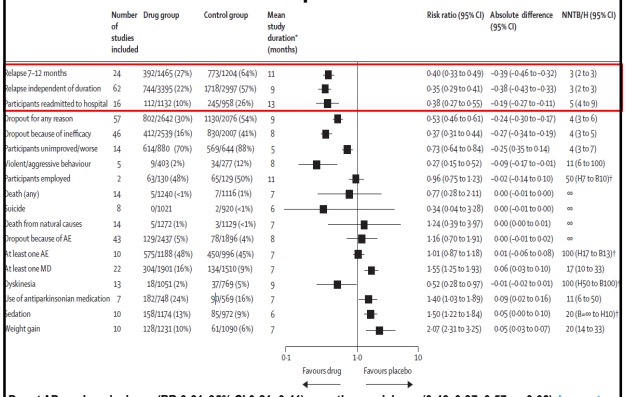
26-Week Schizophrenia Trial of Aripiprazole: "STAR"



P values vs SOC. QLS=Quality of Life Scale (21 items, each scored on a 7-point scale divided into 5 QLS subscales); SOC=olanzapine, quetiapine, risperidone.

Hanssens L et al. Eur Psychiatry. 2008 Aug;23(5):336-43.

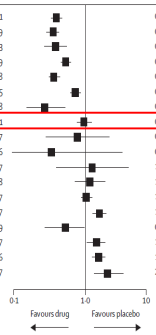
APs vs PBO for Relapse Prevention in SCZ



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

	Number of studies included	Drug group	Control group	Mean study duration* (months)	Risk ratio (95% CI)	Absolute difference (95% CI)	NNTB/H (95% CI)
Relapse 7–12 months	24	392/1465 (27%)	773/1204 (64%)	11	0·40 (0·33 to 0·49)	−0·39 (−0·46 to −0·32)	3 (2 to 3)
Relapse independent of duration	62	744/3395 (22%)	1718/2997 (57%)	9	0·35 (0·29 to 0·41)	−0·38 (−0·43 to −0·33)	3 (2 to 3)
Participants readmitted to hospital	16	112/1132 (10%)	245/958 (26%)	13	0·38 (0·27 to 0·55)	−0·19 (−0·27 to −0·11)	5 (4 to 9)
Dropout for any reason	57	802/2642 (30%)	1130/2076 (54%)	9	0·53 (0·46 to 0·61)	−0·24 (−0·30 to −0·17)	4 (3 to 6)
Dropout because of inefficacy	46	412/2539 (16%)	830/2007 (41%)	8	0·37 (0·31 to 0·44)	−0·27 (−0·34 to −0·19)	4 (3 to 5)
Participants unimproved/worse	14	614/880 (70%)	569/644 (88%)	5	0·73 (0·64 to 0·84)	−0·25 (0·35 to 0·14)	4 (3 to 7)
Violent/aggressive behaviour	5	9/403 (2%)	34/277 (12%)	8	0·27 (0·15 to 0·52)	−0·09 (−0·17 to −0·01)	11 (6 to 100)
Participants employed	2	63/130 (48%)	65/129 (50%)	11	0·96 (0·75 to 1·23)	−0·02 (−0·14 to 0·10)	50 (H7 to B10)†
Death (any)	14	5/1240 (<1%)	7/1116 (1%)	7	0·77 (0·28 to 2·11)	0·00 (−0·01 to 0·00)	∞
Suicide	8	0/1021	2/920 (<1%)	6	0·34 (0·04 to 3·28)	0·00 (−0·01 to 0·00)	∞
Death from natural causes	14	5/1272 (1%)	3/1129 (<1%)	7	1·24 (0·39 to 3·97)	0·00 (0·00 to 0·01)	∞
Dropout because of AE	43	129/2437 (5%)	78/1896 (4%)	8	1·16 (0·70 to 1·91)	0·00 (−0·01 to 0·02)	∞
At least one AE	10	575/1188 (48%)	450/996 (45%)	7	1·01 (0·87 to 1·18)	0·01 (−0·06 to 0·08)	100 (H17 to B13)†
At least one MD	22	304/1901 (16%)	134/1510 (9%)	7	1·55 (1·25 to 1·93)	0·06 (0·03 to 0·10)	17 (10 to 33)
Dyskinesia	13	18/1051 (2%)	37/769 (5%)	9	0·52 (0·28 to 0·97)	−0·01 (−0·02 to 0·01)	100 (H50 to B100)†
Use of antiparkinsonian medication	7	182/748 (24%)	91/569 (16%)	7	1·40 (1·03 to 1·89)	0·09 (0·02 to 0·16)	11 (6 to 50)
Sedation	10	158/1174 (13%)	85/972 (9%)	6	1·50 (1·22 to 1·84)	0·05 (0·00 to 0·10)	20 (B∞ to H10)†
Weight gain	10	128/1231 (10%)	61/1090 (6%)	7	2·07 (2·31 to 3·25)	0·05 (0·03 to 0·07)	20 (14 to 33)



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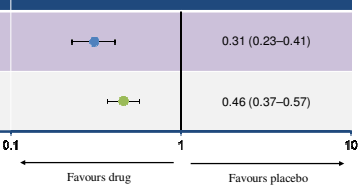
Dropout for any reason	57	802/2642 (30%)	1130/2076 (54%)	9	0·53 (0·46 to 0·61)	−0·24 (−0·30 to −0·17)	4 (3 to 6)
Dropout because of inefficacy	46	412/2539 (16%)	830/2007 (41%)	8	0·37 (0·31 to 0·44)	−0·27 (−0·34 to −0·19)	4 (3 to 5)
Participants unimproved/worse	14	614/880 (70%)	569/644 (88%)	5	0·73 (0·64 to 0·84)	−0·25 (0·35 to 0·14)	4 (3 to 7)
Violent/aggressive behaviour	5	9/403 (2%)	34/277 (12%)	8	0·27 (0·15 to 0·52)	−0·09 (−0·17 to −0·01)	11 (6 to 100)
Participants employed	2	63/130 (48%)	65/129 (50%)	11	0·96 (0·75 to 1·23)	−0·02 (−0·14 to 0·10)	50 (H7 to B10)†
Death (any)	14	5/1240 (<1%)	7/1116 (1%)	7	0·77 (0·28 to 2·11)	0·00 (−0·01 to 0·00)	∞
Suicide	8	0/1021	2/920 (<1%)	6	0·34 (0·04 to 3·28)	0·00 (−0·01 to 0·00)	∞
Death from natural causes	14	5/1272 (1%)	3/1129 (<1%)	7	1·24 (0·39 to 3·97)	0·00 (0·00 to 0·01)	∞
Dropout because of AE	43	129/2437 (5%)	78/1896 (4%)	8	1·16 (0·70 to 1·91)	0·00 (−0·01 to 0·02)	∞
At least one AE	10	575/1188 (48%)	450/996 (45%)	7	1·01 (0·87 to 1·18)	0·01 (−0·06 to 0·08)	100 (H17 to B13)†
At least one MD	22	304/1901 (16%)	134/1510 (9%)	7	1·55 (1·25 to 1·93)	0·06 (0·03 to 0·10)	17 (10 to 33)
Dyskinesia	13	18/1051 (2%)	37/769 (5%)	9	0·52 (0·28 to 0·97)	−0·01 (−0·02 to 0·01)	100 (H50 to B100)†
Use of antiparkinsonian medication	7	182/748 (24%)	91/569 (16%)	7	1·40 (1·03 to 1·89)	0·09 (0·02 to 0·16)	11 (6 to 50)
Sedation	10	158/1174 (13%)	85/972 (9%)	6	1·50 (1·22 to 1·84)	0·05 (0·00 to 0·10)	20 (B∞ to H10)†
Weight gain	10	128/1231 (10%)	61/1090 (6%)	7	2·07 (2·31 to 3·25)	0·05 (0·03 to 0·07)	20 (14 to 33)

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

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)



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

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

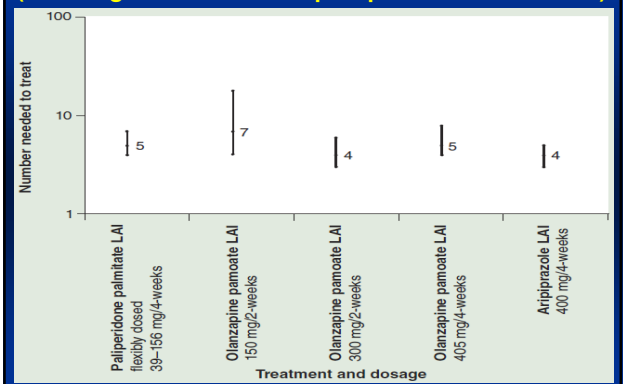
Leucht et al. Lancet 2012;79:2063–2071

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

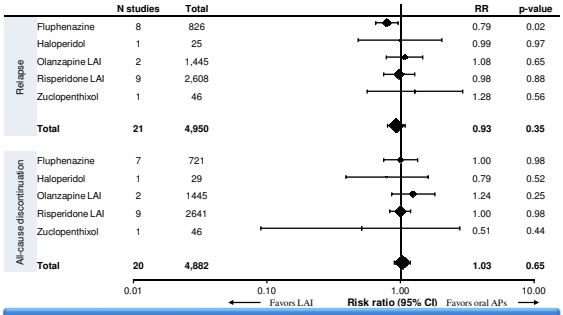
Correll CU et al. J Clin Psychiatry. 2016;77(suppl 3):1-24.

Prevention of Relapse with LAIs vs Placebo (vs 45 mg / 4 weeks Olanzapine pamoate for OLA-LAI)



LAI= long-acting injectable antipsychotic Citrome L. et al. Expert Rev Neurother. 2013 Jul;13(7):767-83.

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



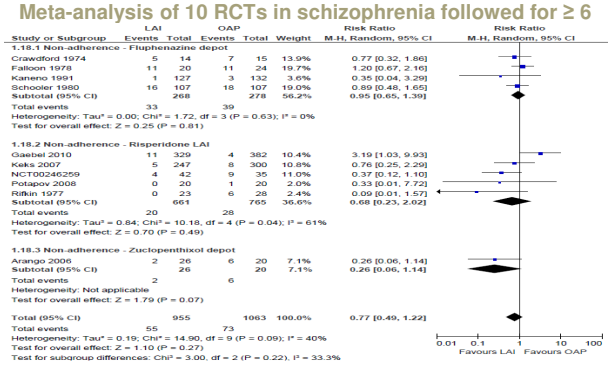
No difference in adherence between pooled LAIs and oral APs (measured in 10 studies)

AP, antipsychotic; CI, confidence interval; LAI, long-acting injectable antipsychotic; 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.

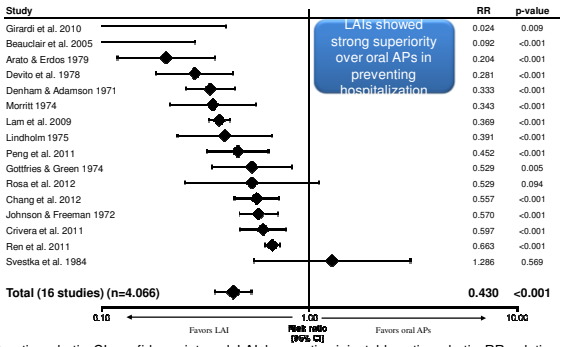
LAIs Were not Superior to Oral Antipsychotics Regarding Adherence

Meta-analysis of 10 RCTs in schizophrenia followed for ≥ 6



Kishimoto T, et al. Schizophr Bull. 2014 Jan;40(1):192-213.

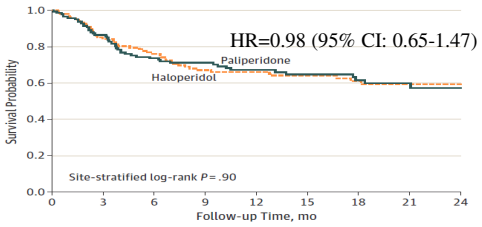
In Mirror Image Studies, LAIs reduce risk of hospitalization compared with oral antipsychotics



AP, antipsychotic; CI, confidence interval; LAI, long-acting injectable antipsychotic; RR, relative risk
25 studies, N=5,940

Kishimoto T, Nitta M, Borenstein M, Kane JM, Correll CU. J Clin Psychiatry. 2013 Oct;74:957-65.

Paliperidone LAI vs Haloperidol LAI: Time to Efficacy Failure



No. at risk									
Paliperidone	145	119	91	76	62	51	36	26	10
Haloperidol	145	107	88	71	64	51	39	30	13
No. with event									
Paliperidone	0	19	36	39	43	45	47	48	49
Haloperidol	0	21	31	41	42	44	46	47	47

Efficacy failure (independent committee): psychiatric hospitalization; need for crisis stabilization; meaningful increase in outpatient visits; inability to discontinue oral antipsychotics within 8 weeks due to insufficient benefit; discontinuation of LAI due to insufficient benefit; ongoing or repeated need for oral antipsychotics beyond 8 weeks

McEvoy J et al. JAMA 2014;311(19):1978-86.

Paliperidone LAI vs Haloperidol LAI: Cardiovascular Adverse Effects

Outcome	Paliperidone Palmitate (n = 147)	Haloperidol Decanoate (n = 147)	*P* Value[a]
Weight change (least-squares mean) from baseline, mean (95% CI), kg			
Month 6	2.17 (1.25 to 3.09)	−0.96 (−1.88 to −0.04)	<.001[b]
Month 12	3.46 (1.83 to 5.09)	−1.93 (−3.56 to −0.31)	
Month 18	4.75 (2.36 to 7.14)	−2.91 (−5.28 to −0.53)	
Month 24	6.04 (2.88 to 9.20)	−3.88 (−7.02 to −0.73)	
Ever gained ≥15 lbs from baseline, No. (%)	48 (33.1)	32 (22.4)	.03[c]
At least 1 laboratory assessment after first injection, No. of patients	129	126	
Laboratory values, worst change from baseline			
Results, least-squares mean (95% CI)			
HbA_{1c}, %	0.34 (0.17 to 0.52)	0.23 (0.06 to 0.41)	.38[d]
Blood glucose, mg/dL	21.13 (12.59 to 29.67)	20.96 (12.38 to 29.54)	.98[d]
Total cholesterol, mg/dL	12.42 (7.20 to 17.63)	16.82 (11.56 to 22.07)	.25[d]
LDL cholesterol, mg/dL	11.70 (7.06 to 16.34)	13.49 (8.85 to 18.14)	.59[d]
Triglycerides, mg/dL	36.91 (22.40 to 51.43)	46.57 (31.93 to 61.21)	.36[d]
HDL cholesterol, mg/dL	−5.28 (−6.74 to −3.83)	−4.52 (−5.98 to −3.05)	.47[d]

McEvoy J et al. JAMA 2014;311(19):1978-86.

Paliperidone LAI vs Haloperidol LAI: Neuromotor and Prolactin-Related Adverse Effects

Outcome	Paliperidone Palmitate (n = 147)	Haloperidol Decanoate (n = 147)	*P* Value[a]
Neurologic effects			
AIMS global severity score			
Incidence of AIMS ≥2, No. (%)	28 (21.4)	30 (23.8)	0.57[c]
Worst change from baseline, least-squares mean (95% CI)	0.43 (0.31 to 0.55)	0.50 (0.38 to 0.62)	.39[d]
BAS global score			
Incidence of BAS ≥3, No. (%)	4 (2.8)	15 (10.6)	.006[c]
Worst change from baseline, least-squares mean (95% CI)	0.45 (0.31 to 0.59)	0.73 (0.59 to 0.87)	.006[d]
SAS mean score			
Incidence of SAS ≥1, No. (%)	109 (79.0)	101 (74.8)	.45[c]
Worst change from baseline, least-squares mean (95% CI)	0.21 (0.16 to 0.27)	0.25 (0.20 to 0.30)	.34[d]
Serum prolactin levels			
Among men only			
Highest level after baseline, least-squares mean (95% CI), µg/L	34.56 (29.75 to 39.37)	15.41 (10.73 to 20.08)	<.001[e]
Worst ASEX after baseline, least-squares mean (95% CI)[f]	17.68 (16.36 to 19.00)	17.95 (16.66 to 19.25)	.77[e]
ASEX score ≥19, No. (%)	34 (37.8)	37 (39.4)	.72[c]
Incidence of gynecomastia or galactorrhea, No. (%)[g]	5 (4.7)	3 (2.8)	.46[h]
Among women only			
Highest level after baseline, least-squares mean (95% CI), µg/L	75.19 (63.03 to 87.36)	26.84 (13.29 to 40.40)	<.001[e]
Worst ASEX after baseline, least-squares mean (95% CI)[f]	23.41 (21.01 to 25.80)	22.83 (20.12 to 25.54)	.75[e]
ASEX score ≥19, No. (%)	24 (72.7)	19 (73.1)	.88[c]
Incidence of gynecomastia, galactorrhea, or menstrual irregularities, No. (%)[i]	10 (38.5)	5 (29.4)	.13[c]

McEvoy J et al. JAMA 2014;311(19):1978-86.

QUALIFY Study - Aripiprazole Once-monthly and Paliperidone Palmitate Once-Monthly: Study Design

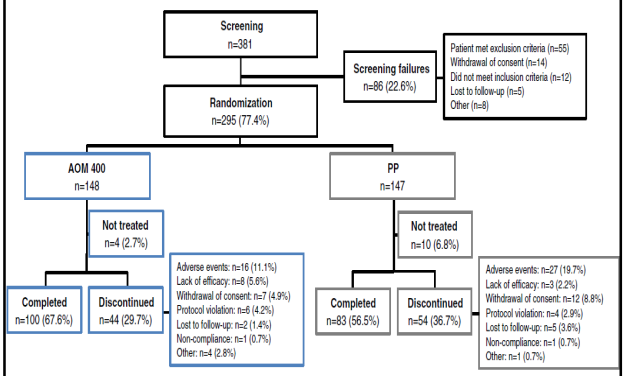
- *Design:* randomized, open-label rater-blinded, head-to-head comparison of intramuscular aripiprazole once-monthly (400 or 300 mg/month) and intramuscular paliperidone palmitate injection (50 to 150 mg/month)
- Non-inferiority study, allowing for subsequent superiority testing, if non-inferiority criterion was met
- Population: 18-60 years with a diagnosis of schizophrenia (predefined age stratification (18- ≤ 35 vs >35-60)
- CGI-S Score ≥ 3 (mildly ill) and ≤ 5 (markedly ill)
- Reason for change in treatment (inefficacy, intolerability, poor adherence)
- Duration: 28 weeks (3-week oral conversion period, 5-week intramuscular formulations, continued for 20 weeks.
- Primary outcome: Heinrichs-Carpenter Quality of Life Scale (QLS)
  - intrapsychic foundations (sense of purpose, motivation, emotional interaction, etc.)
  - interpersonal relations (social activity, social network, etc.)
  - instrumental role (work functioning, work satisfaction, etc.)
  - common objects and activities (self-care, hobbies).

  75% functional
- Key secondary outcome: Clinical Global Impressions scales (CGI),

Naber D, et al. Schizophr Res. 2015 Oct;168(1-2):498-504.

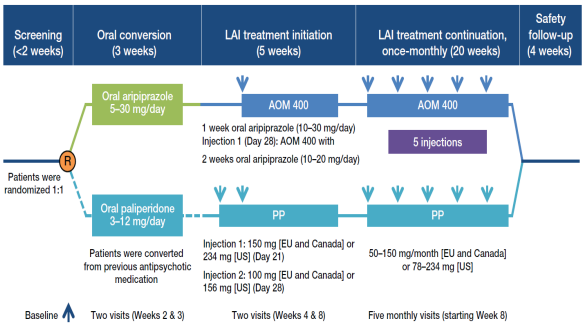
4

QUALIFY: Patient Disposition



Naber D, et al. Schizophr Res. 2015 Oct;168(1-2):498-504.

QUALIFY Study Design: ARI LAI vs PALI LAI

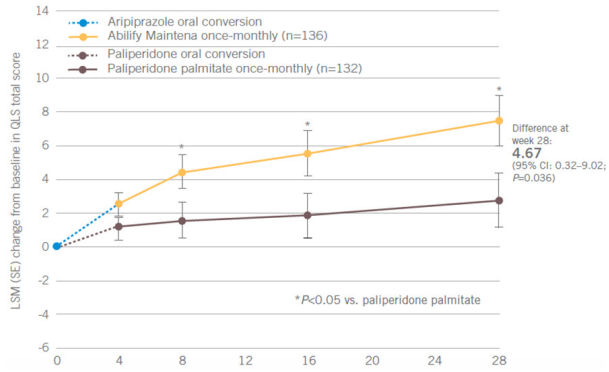


[a]Patients underwent screening for eligibility (7–14 days). LAI: long-acting injectable. R: randomization

Naber D, et al. Schizophr Res. 2015 Oct;168(1-2):498-504

QUALIFY: ARI LAI vs PALI LAI: Primary Outcome

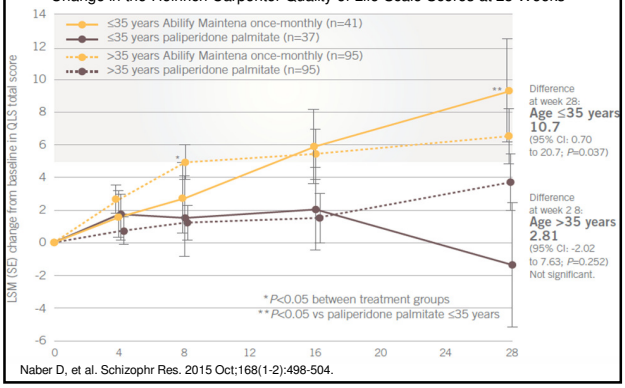
Change in the Heinrichs-Carpenter Quality of Life Scale Scores at 28 Weeks



Naber D, et al. Schizophr Res. 2015 Oct;168(1-2):498-504.

ARI LAI vs PALI LAI (QUALIFY): QLS By Prespecifid Age Group

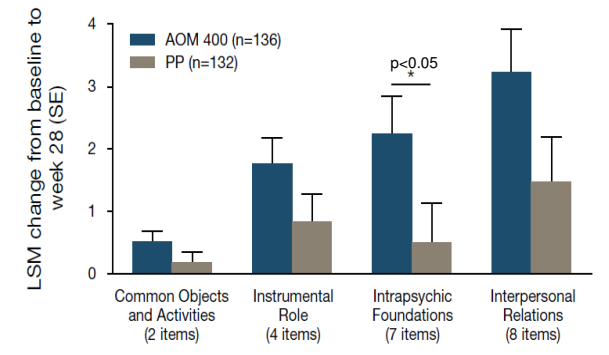
Change in the Heinrich Carpenter Quality of Life Scale Scores at 28 Weeks



Naber D, et al. Schizophr Res. 2015 Oct;168(1-2):498-504.

QUALIFY: ARI LAI vs PALI LAI: QLS Domains

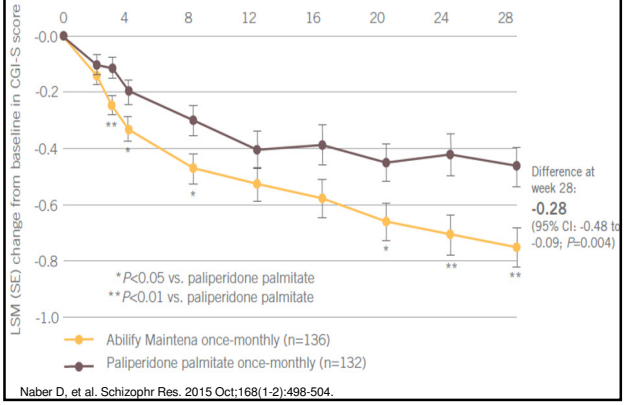
Significantly greater improvement in Intrapsychic Foundations with ARI LAI at 28 weeks



Naber D, et al. Schizophr Res. 2015 Oct;168(1-2):498-504.

ARI LAI vs PALI LAI (QUALIFY): CGI-S

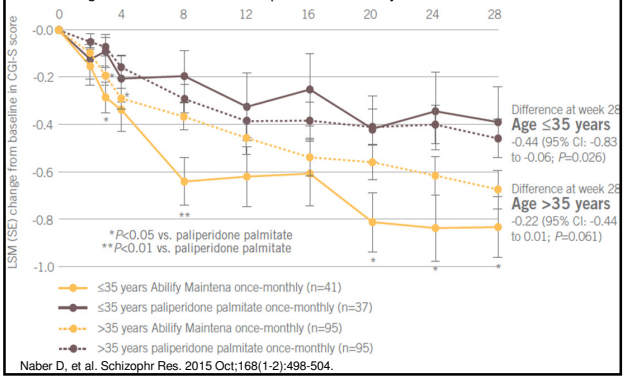
Change in the Clinical Global Impressions Severity Scale Scores at 28 Weeks



Naber D, et al. Schizophr Res. 2015 Oct;168(1-2):498-504.

ARI LAI vs PALI LAI (QUALIFY): CGI-S By Prespecifid Age Group

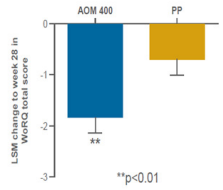
Change in the Clinical Global Impressions Severity Scale Scores at 28 Weeks



Naber D, et al. Schizophr Res. 2015 Oct;168(1-2):498-504.

Aripiprazole Once Monthly: Significantly greater Improvement in Work Readiness Questionnaire Total Scores vs. Paliperidone Once Monthly

WoRQ total scores



WoRQ status shift table

Shift table of status on Readiness for work (Yes/No) – WoRQ item 8

		AOM 400 (n=110)		PP (n=98)	
		Baseline:			
		Yes (n=36)	No (n=74)	Yes (n=29)	No (n=69)
Week 28:	Yes	29 (81%)	29 (39%)	20 (69%)	12 (17%)
	No	7 (19%)	45 (61%)	9 (31%)	57 (83%)

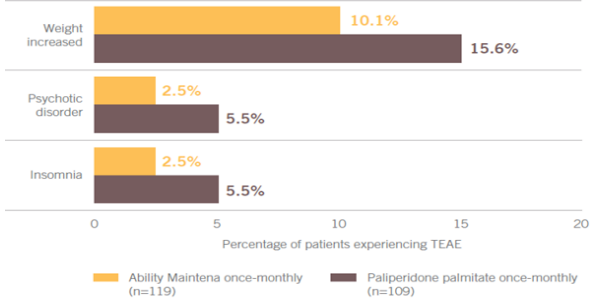
- The odds at week 28 of being rated ready for work were significantly higher for AOM 400 vs PP (adjusted odds ratio: 2.67, 95%CI: [1.39;5.14], p=0.003)

**p<0.01 indicates significant differences between treatments (AOM 400 vs PP) analysed with MMRM in FAS

Adapted from Naber D, et al. ASCP 2015, Miami, Florida, USA. Poster 87.

Aripiprazole Once Monthly: Adverse Effect Advantages Over Paliperidone Once Monthly

Treatment-emergent adverse events (TEAEs) occurring in ≥5% of patients in the treatment continuation phase (period c)



Naber D, et al. Schizophr Res. 2015 Oct;168(1-2):498-504.

Aripiprazole Once Monthly: Lower Rate of Sexual Dysfunction Than Paliperidone Once Monthly Injection

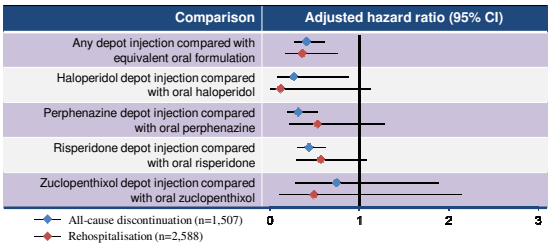
Adjusted odds ratios (OR) for the risk of ASEX-assessed sexual dysfunction at baseline and after 28 weeks treatment with AOM 400 or paliperidone palmitate (PP)

Incidence of sexual dysfunction, n/N (%)	AOM 400	PP	Adjusted OR [95% CI]	P-value
All patients: Baseline	56/103 (54.4)	55/84 (65.5)		0.14*
Males, baseline	30/61 (49.2)	25/46 (54.3)		0.70*
Females, baseline	26/42 (61.9)	30/38 (78.9)		0.14*
All patients: Week 28	39/103 (37.9)	53/84 (63.1)	0.29 [0.14;0.61]	0.0012
Males	17/61 (27.9)	23/46 (50.0)	0.33 [0.13;0.86]	0.023
Females	22/42 (52.4)	30/38 (78.9)	0.14 [0.03;0.62]	0.0099

Sexual dysfunction pre-defined as an ASEX total score of ≥19, or a score of ≥5 on any one item, or a score of ≥4 on at least 3 items.
*p-value derived from Fisher's exact test. Results shown from the full analysis set.
Potkin et al. Presented at the 28th annual European College of Neuropsychopharmacology (ECNP) congress; August 31–September 1, 2015; Amsterdam, The Netherlands. P.3.d.078.

LAI antipsychotics significantly improve treatment outcomes in patients with schizophrenia

Risk of discontinuation or rehospitalisation after a first hospitalisation 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

Adverse Effects

Time Course of Antipsychotic Adverse Effects

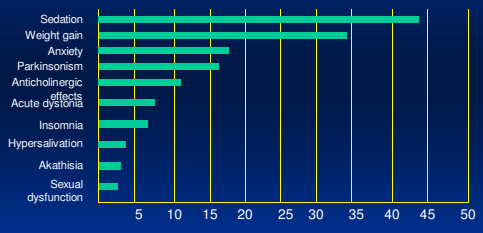
Receptor	Acute: ≤1 wk	Consequence	Early: <3 mo	Consequence	Late: ≥3 mo	Consequence
α 1	Hypotension*	Falls non-adherence	Hypotension *	Falls non-adherence	Hypotension	Falls non-adherence
D 2	Dystonia * Parkinsonism*	Pain non-adherence	Parkinsonism* Akathisia *	↓cognition non-adherence	TD	Stigma ↓socialization ↓quality of life
	↑ Prolactin (*)	Sexual Dysfunction non-adherence	↑ Prolactin (*)	Sexual Dysfunction Hypogonadism non-adherence	↑ Prolactin	Osteoporosis ? CHD ? breast cancer
H 1	Sedation *	↓cognition ↓functioning non-adherence	Sedation *	↓cognition ↓functioning non-adherence	Sedation	↓cognition ↓functioning non-adherence
	↑ Weight	↑ lipids/ glucose	↑ Weight	↑ lipids/glucose non-adherence	Diabetes dyslipidemia CHD	↓functioning ↓quality of life early death
M 1-4	Blurry vision* dry mouth *	Discomfort non-adherence	↓cognition Blurry vision * dry mouth * constipation*	↓functioning discomfort non-adherence	↓cognition Blurry vision * dry mouth * constipation*	↓functioning discomfort non-adherence

Acute (<1 week) Early (<3 months) Late

*= Tolerance may develop; CHD= Coronary heart disease Correll CU. CNS Spectr. 2007;12(12) (Suppl 21):10-14.

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

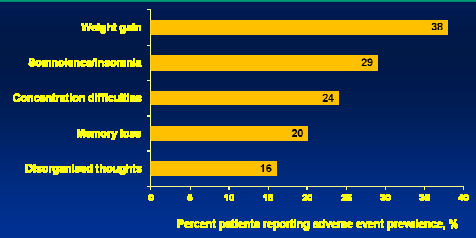


Angermeyer MC *et al. Psychiat Prax* 1999;26:171–4

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

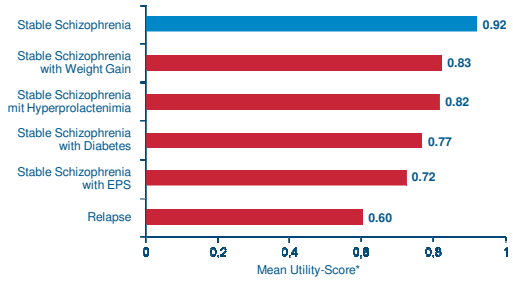
UNITE survey was an internet-based multinational survey with 1,300 respondents with bipolar disorder from 11 countries

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



McIntyre RS. *J Clin Psychiatry*. 2009;70 Suppl 3:5–11.

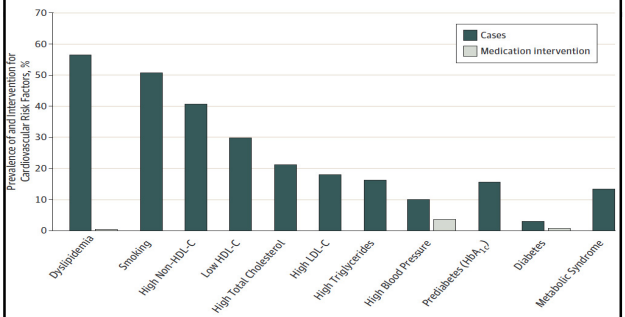
Relapse and Adverse Efffects Reduce Quality of Life in Patients with Schizophrenia



*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

RAISE: Baseline rates of smoking, lipid abnormalities, hypertension diabetes + metabolic syndrome +/- medication intervention



After 47 days average lifetime antipsychotic treatment, olanzapine and quetiapine were related to higher metabolic values; dyslipidemia: TC ≥200 mg/dL or TG ≥150 mg/dL, or low HDL;
TC=total cholesterol; TG=triglyceride; HDL=high-density lipoprotein; LDL=low-density lipoprotein

Correll CU et al. JAMA Psychiatry 2014 Dec 1;71(12):1350-63.

Diabetes Risk in 7,139 FE SCZ Pts, Followed for 6.6 Yrs (47,297 Pt-yrs)

Factors associated with altered risk for type 2 diabetes during the last 3 months of follow-up

	Adjusted for observation time				
Variable	OR	z	*p*	95% CI	
Aripiprazole	0.53	-2.8	0.005	0.34	0.82
Receiving no antipsychotics	0.60	-2.97	0.003	0.43	0.84
Percentage of time being hospitalized*	NS				
Age of first prescription of antipsychotics*	1.01	3.53	0.001	1.01	1.02
Olanzapine	1.57	2.97	0.003	1.17	2.11
Low-potency FGA	1.45	2.44	0.015	1.08	1.96
Clozapine	2.31	4.12	0.001	1.55	3.44

AP: antipsychotic; FGA: first-generation antipsychotic
*Percentage of time being hospitalized is used as a continuous variable, that is odds ratio (OR) indicates increase from, for example, 2 to 3% and so on.

Nielsen J, Skadhede S, Correll CU. Neuropsychopharmacology. 2010 Aug;35(9):1997-2004.

Diabetes Risk Increases with Increasing Dose with Olanzapine, Quetiapine and Risperidone

Dose category	Patients exposed (N)	Events (N)	Person-years	Diabetes rate (per 100 person-years)	Adjusted[c] HR[d] (95% CI*)
Aripiprazole					p[f] = 0.43
≥15 mg	1321	4	371	1.1	1.3 (0.1, 12.2)
10 - <15 mg	988	1	214	0.5	0.6 (0.04, 9.8)
<10 mg	788	1	145	0.7	Reference
Olanzapine					p[f] = 0.002
≥10 mg	5921	58	2176	2.7	2.5 (1.4, 4.5)
5 - <10 mg	6761	41	2118	1.9	1.7 (1.0, 3.1)
<5 mg	4398	15	1361	1.1	Reference
Quetiapine					p[f] = 0.007
>150 mg	4686	34	1686	2.0	2.5 (1.3, 4.7)
51 -150 mg	5525	15	1610	0.9	1.2 (0.6, 2.5)
≤50 mg	6516	13	1838	0.7	Reference
Risperidone					p[f] = 0.10
≥ 2 mg	5103	23	1852	1.2	2.1 (1.0, 4.4)
1 - <2 mg	5187	15	1649	0.9	1.4 (0.6, 3.1)
<1 mg	4353	10	1372	0.7	Reference
Ziprasidone					p[f] = 0.60
>80 mg	624	1	186	0.5	0.3 (0.03, 3.4)
41 - 80 mg	671	2	170	1.2	0.6 (0.1, 4.0)
≤40 mg	725	3	181	1.7	Reference

Doses expressed in tertiles

Ucickas Yood M et al. BMC Psychiatry. 2011 Dec 15;11:197.

Body Mass Index Identified as an Independent Predictor of Psychiatric Readmission

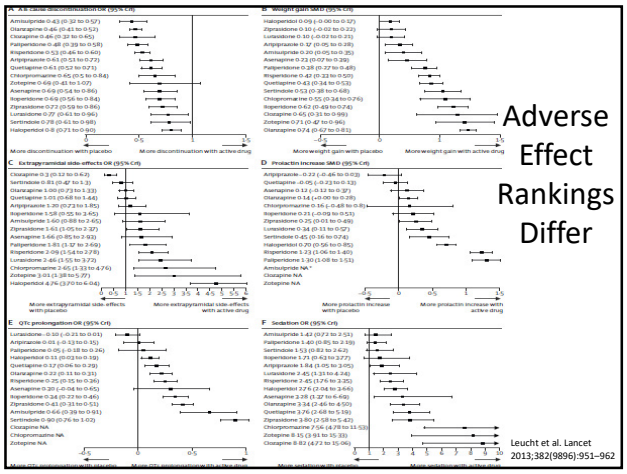
Peter Manu, MD; Sameer Khan, MD; Rajiv Radhakrishnan, MBBS; Mark J. Russ, MD; John M. Kane, MD; and Christoph U. Correll, MD

Method: After identifying univariate correlates of readmission, we used logistic regression with backward elimination to identify independent predictors of readmissions within 1 year after the index psychiatric hospitalization.

Results: Among 224 (23.7%) of 945 readmitted patients, psychiatric readmission was significantly associated with age ($P = .0029$), length of stay ($P = .036$), schizophrenia/schizoaffective disorder ($P < .0001$), dementia ($P = .027$), major depressive disorder ($P = .0006$), treatment with atypical antipsychotic drugs ($P = .0054$), electroconvulsive therapy ($P < .0001$), and BMI ($P = .0079$), but not with physical comorbidities and routine laboratory data. The independent predictors of readmission were higher BMI (median = 28.5 kg/m^2; odds ratio [OR] = 3.6; CI, 1.2–10.6), a diagnosis of schizophrenia/schizoaffective disorder (OR = 2.2; CI, 1.5–3.4), clozapine treatment (OR = 2.8; CI, 1.1–6.9), no electroconvulsive therapy (OR = 0.13; CI, 0.02–0.45), and shorter length of stay (median = 18 days; OR = 0.08; CI, 0.01–0.42).

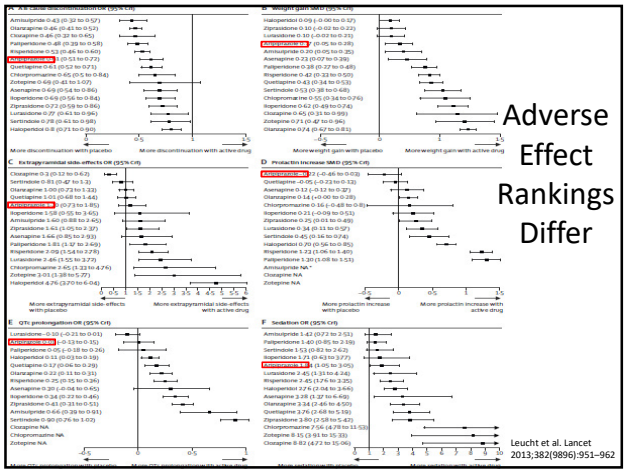
Conclusions: Body mass index was identified, for the first time, as an independent predictor of psychiatric rehospitalization. Enhanced outpatient treatment programs for overweight and obese psychiatric patients might influence readmission rates and should be explored in prospective studies.

J Clin Psychiatry 2014;75(6):e573–e577



Adverse Effect Rankings Differ

Leucht et al. Lancet 2013;382(9896):951–962



Adverse Effect Rankings Differ

Leucht et al. Lancet 2013;382(9896):951–962

Conclusions

- Schizophrenia is a severe disorder that often has a chronic and debilitating course
- Due to lack of reliable intra-individual response predictors, antipsychotic choice needs to be tailored to patient characteristics and needs
- Efficacy differences are considerably smaller and less predictable than adverse effect differences (except for clozapine in refractory patients)
- Long-term outcomes, including tolerability, are significant determinants in individualized treatment
- Maintenance treatment and relapse prevention are preeminent goals to improve outcomes
- Quality of life and subjective well-being need to be targeted and studied more

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