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Supplementary Material

Article Title: The Use of Long-Acting Injectable Antipsychotics in Schizophrenia: Evaluating the Evidence

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Supplementary eTable 1. Summary of Mirror-Image Studies

Study/ Country	N[a]	Data Source	LAI Phase	Follow-Up Duration, mo Oral AP/LAI	Inclusion Criteria	Reported Outcome	Age, y (mean ± SD)	% Male	Chronicity	Medication: LAI (n)[b] / Oral AP (n)[b]	Medication: Dose, mg (mean ± SD)	Key Outcomes
Chang et al[48] 2012/Taiwan	184	Medical claims data, nationwide	Retrospective, dropouts excluded	12/12	SCZ (*ICD-9*), started RLAI, followed ≥ 1 y before and after RLAI initiation, treated regularly with RLAI	# Hps # Outpatient visits # ER visits % Hps[c] # Hp days # Relapse Cost	36–55[d]	50.5	DOI ≥ 6 y in 77.2%	RLAI (184) CLO (7) RIS (80) Other SGA (50) Oral FGA (91)	total 177/3 mo NR	Reduction of 34% and 32% of total inpatient services costs and inpatient nonmedication costs, respectively ($P < .005$) Overall psychiatric service costs increased 26%
Rosa et al[49] 2012/Int.	98	Multinational	Prospective, dropouts excluded	6/6	SCZ/SzAD (*DSM-IV*), nonacute, previously treated with OLA (stable dose) and willing to switch to RLAI, not known as RIS nonresponder	# Experienced Hps # Experienced Hps due to psychotic disease # Experienced relapses # Hp days Psychopathology Social functioning Safety measures	40.2 ± 14.0[e]	77.1[e]	Mean DOI: 13.5 y[e]	RLAI (79) OLA (79)	32.6 ± 7.1/ 2 wk 16.2 ± 5.6	Significant efficacy changes vs baseline were observed for PANSS, CGI-S, and GAF (all $P < .0001$) TEAEs were similar with 1 wk and 3 wk OLA taper (40.0% and 46.5%, respectively) TEAEs were generally mild (34.5%) or moderate (49.0%) in intensity
Crivera et al[50] 2011/USA	435	Multicenter	Prospective, dropouts included	12/1[f]	SCZ (*DSM-IV*), appropriate for RLAI initiation	# Hps # Psychiatric Hps # ER visits % Psychiatric Hps	41.9 ± 12.6	66.7	Mean ± SD DOI: 17.6 ± 12.1 y	RLAI (435, 343) NR (435, 343)	25/2 wk NR	Annual number of Hps (for any reason and psychiatric Hps) and ER visits decreased significantly after initiation of RLAI (all P values <.0001)
Ren et al[51] 2011/USA	924	VA, multicenter	Retrospective, dropouts included	12/12	SCZ (*ICD-9*), started RLAI, and had ≥ 4 RLAI injections	# Psychiatric Hps % Psychiatric Hps % ≥ 2 Psychiatric Hps # Hp days Length of stay	51 ± 11	94	NR	RLAI (924) NR (924)	38.9 ± 13.0/ 2 wk NR	Initiation of RLAI associated with significant reductions in number of psychiatric Hps, % of patients hospitalized, # Hp days, and length of stay
Peng et al[52] 2011/USA	147	Commercial claims data, multicenter	Retrospective, dropouts included	6/6	SCZ (*ICD-9*), started any depot, but without depot injection in the 6 mo before baseline, ≥ 2 outpatient visits or ≥ 1 Hp within 180 d	# Hps % Hps % Psychiatric Hps % Hps for SCZ # Hp days # Psychiatric Hp days # Hp days for SCZ	42.6 ± 14.7	53.7	NR	RLAI (38) HAL (69) FPZ (40) NR (147)	NR NR	Psychiatric Hps decreased from 49.7% before depot initiation to 22.4% after depot initiation Decreases also noted for total Hps, SCZ-related Hps, and total health care costs

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Carswell et al[53] 2010/New Zealand	443	Multicenter (5 centers)	Retrospective, dropouts included	12/12	SCZ (*DSM-IV*), nonadherent to oral AP (or preferred RLAI), intensive treatment in the year prior to switching to RLAI	# Hps # Hp days # Days of compulsory treatment order Cost	35.9 ± 12.4	64.3	Mean ± SD DOI: 11.7 ± 9.9 y	RLAI (427) NR (427)	41.5/2 wk[g] NR	The mean number of Hp admissions was significantly lower post-RLAI than pre-RLAI (1.38 vs 0.61, $P < .001$), although mean length of stay was longer and mean costs were also lower
Girardi et al[54] 2010/Italy	88	Multicenter	Prospective, no dropouts during the 6-month phase	6/6 (24)[f]	SCZ/SzAD (*DSM-IV*), with clinically inadequate response to ≥2 oral APs within 3 mo, BPRS total score ≥ 65	% Hps Response rate Psychopathology Safety	41.2 ± 10.6	64.8	Mean ± SD DOI: 18 ± 5.0 y, Mean ± SD # Hp: 8.26 ± 2.79	RLAI (88) OLA (29) CLO (26) QUE (21) HAL (13) ARI (9) RIS (2)	47.4 ± 10.1/ 2 wk NR	Transition to RLAI was associated with improvement on all outcomes studied, including BPRS scores and hospitalization AEs were reduced by 2.5- to 7.4-fold during 18 mo of follow-up with RLAI
Su et al[55] 2009/Taiwan	108	Medical claims data, nationwide	Retrospective, dropouts excluded	12/12	SCZ (*ICD-9*), regularly treated with RLAI for ≥1 y, ≥1 y data in pre-RLAI periods, had < 90 d Hps	# Hps # ER visits # Hp days # Relapses	42.0 ± 10.4	50	NR	RLAI (108) RIS (17) Other SGA (41) FGA (27) FGA + RIS (10) FGA + other SGA (5) None (8)	175.4 ± 54.5/ 3 mo NR	Switching to RLAI was associated with significant reductions in the total annual numbers of acute hospital admissions (55% reduction, $P = .0003$), Hp days (48% reduction, $P = .0021$), and relapses (54% reduction, $P = .0005$)
Lam et al[56] 2009/15 countries	2,300	Multinational	Prospective, dropouts included	12/12	SCZ who participated in RLAI clinical trials	% Hps All cause discontinuation Psychopathology	38.4	NR	Mean DOI: 10.3 y	RLAI (1,748) OAP (1,748)	NR NR	12-mo Hp rate was 44.5% on oral AP vs 16.4% on RLAI ($P < .001$)
Fuller et al[57] 2009/USA	106	VA (Ohio), multicenter (5 centers)	Retrospective, dropout included	10.2 ± 6.4/ 10.2 ± 6.4 (mean ± SD)	SCZ/SzAD (*ICD-9*) at any time of the study period (1/2003 to 1/2006), with continuous enrolment throughout the study period, ≥4 injections of RLAI	# Psychiatric Hps % Psychiatric Hps % ≥ 2 Psychiatric Hps # Psychiatric Hp days # Psychiatric Hp days/ months # Psychiatric-related outpatient visits Compliance Cost	51.9 ± 10.2	93	NR	RLAI (106) ARI (7) OLA (19) QUE (30) RIS (57) ZIP (8)	35.5/ 2 wk (end) 26.3 ± 4.9 15.1 ± 7.1 423.5 ± 275.5 3.8 ± 1.9 107.7 ± 45.1	Fewer patients had psychiatric Hps after switch to RLAI (75% vs 42%, $P < .001$) Post-switch patients also had significantly lower mean number and duration of Hps

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Supplementary eTable 1 (continued). Summary of Mirror-Image Studies

Study/ Country	N[a]	Data Source	LAI Phase	Follow-Up Duration, mo Oral AP/LAI	Inclusion Criteria	Reported Outcome	Age, y (mean ± SD)	% Male	Chronicity	Medication LAI (n)[b] / Oral AP (n)[b]	Medication Dose, mg (mean ± SD)	Key Outcomes
Beauclair et al[58] 2005/Canada	63	Multicenter	Retrospective, dropouts included	39.4/ 40.3	SCZ who participated in RLAI clinical trials	# Hps % Hps % Experienced ≥ 2 Hps # Hp days All cause discontinuation Concomitant anticholinergic/ anxiolytic/ sedative	NR	NR	NR	RLAI (63) NR (63)	NR NR	Hp rate was lower after initiation of RLAI (52.4% vs 4.8% of patients, $P < .0001$). RLAI was also associated with decreased number of patients with multiple Hps, duration of Hps, and use of concomitant medications (eg, anxiolytics)
Bourin et al[59] 1998/France	48	Single center	Retrospective, dropouts excluded	62.4 ± 33.6/ 69.6 ± 38.4 (mean ± SD)	SCZ (*ICD-10*), hospitalized	# Hps # Hp days	NR	50	NR	FGA (44) OAP (48)	NR NR	Mean number of Hps was higher during depot treatment than during treatment with oral APs (4.8 vs 7.2 Hps), as was the mean number of Hps per year (0.93 vs 1.25)
Svestka et al[60] 1984/Czech	34	Single center	Prospective, dropouts included	10.3/10.3	SCZ, in remission	% Hps	37.4	23.5	Mean DOI: 9.2 y, # Hps in lifetime: 1–12	Clopenthixol decanoate (34) NR	169.5/3.7 wk NR	Lower Hp risk while on LAI than on oral AP (risk ratio = 0.43, $P < .0001$).
Waldmann and Neumann[61] 1984/Germany	65	Single center	Retrospective, dropouts excluded	31.2/31.2	SCZ/SzAD, outpatients and patients in day hospital who were receiving FPZ decanoate	# Hps	NR	27.7	Duration of treatment: 1–9 y	FPZ (65) NR (65)	17.7/3 wk NR	Lower number of Hps while on LAI than on oral AP (rate ratio = 0.0201, $P < .0001$).
Michel et al[62] 1981/Chile	112	Single center	Retrospective, dropouts excluded	12–17/12–17 (range)	SCZ, on depot when study was conducted	# Hp days	25–44[h]	67.9	NR	FPZ NR	NR NR	93% of patients had less medical resource use (eg, nursing consultations, injections, use of concomitant medications) after switching to LAI FPZ, and 96% of patients had fewer consultations after switching

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Study/ Country	N[a]	Data Source	LAI Phase	Follow-Up Duration, mo Oral AP/LAI	Inclusion Criteria	Reported Outcome	Age, y (mean ± SD)	% Male	Chronicity	Medication: LAI (n)[b] Oral AP (n)[b]	Medication: Dose, mg (mean ± SD)	Key Outcomes
Tan et al[63] 1981/Singapore	127	Multicenter (6 centers)	Retrospective, dropouts excluded	24/24	SCZ, DOI ≤ 8 y, ≥ 24 mo treatment before and after the institution of FPZ depot	# Hps # Hp days Compliance	32.5 ± 8.8	61.4	6–8 y	FPZ (127) NR (127)	25/mo NR	Of 127 patients, 105 had reductions in relapses requiring readmission after switching to depot FPZ. Relapses increased in 19 patients and were unchanged in 3.
Arató and Erdós[64] 1979/Hungary	51	Single center	Retrospective, dropouts excluded	44/26	SCZ/SzAD, ≥1 y on depot, ≥2 Hps in the past	# Hps # Patients who experienced Hps	34	100	Mean DOI: 7.2 y	Mixed FGA NR	FPZ (12.5–25 mg/ 4 wk), Flupenthixol (20 mg/3 wk) NR	During LAI treatment, patients had lower incidence of Hp (risk ratio = 0.204, $P < .0001$) and # Hps (rate ratio = 0.106, $P < .0001$)
Devito et al[65] 1978/USA	122	Single center	Retrospective, dropouts excluded	12/12	SCZ spectrum disorders, treated in the same inpatient program and referred for outpatient treatment in the FPZ program	# Hps % Hps Length of stay # Hps per patient	18–39[i]	50.8	NR	FPZ (61) NR (61)	37.5 mg/ 3–4 wk NR	Hp readmission rate was 25% with FPZ vs 44% with oral AP. FPZ group also had shorter mean length of stay (7 vs 20 d)
Polonowita and James[66] 1976/New Zealand	43	Single center	Retrospective, dropouts included	13/13	SCZ (*ICD-8*), started FPZ depot	# Hps # Hp days	NR	67.4	NR	FPZ decanoate (43) NR (43)	NR NR	FPZ associated with significantly fewer Hps (total of 60 vs 22 admissions for oral AP vs FPZ groups, $P < .004$) and a lower mean # Hp days (1,463 vs 327, $P < .00005$)
Lindholm[67] 1975/Sweden	24	Multicenter (2 centers)	Retrospective, dropouts excluded	26.9/26.9	SCZ, administered perphenazine enanthate for > 1 y	# Hps % Hps # Hp days Concomitant antiparkinson medication	44.9	25.0	Mean DOI: 6.8 y	Perphenazine enanthate (24) NR (24)	107 mg NR	Mean # Hps per year decreased from 1.31 during the control period to 0.59 during treatment with perphenazine enanthate ($P < .05$). Perphenazine enthanate was also associated with fewer total Hp days.
Gottfries and Green[68] 1974/Sweden	58	Single center	Retrospective, dropouts excluded	NR	SCZ, discharged, treated with flupenthixol decanoate during observation period	# Relapses requiring Hp % Hps # Hp days Length of stay All cause discontinuation	NR	NR	Patients started LAI during Hp and later were transferred to ambulant treatment	FPZ decanoate (58) NR (58)	40/2 wk as a general rule, (range, 20–60 mg) NR	Significant reduction in relapse frequency after switching from oral APs FPZ decanoate ($P < .005$) Patients also had fewer Hps and shorter duration of stay after switching

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Supplementary eTable 1 (continued). Summary of Mirror-Image Studies

Study/ Country	N[a]	Data Source	LAI Phase	Follow-Up Duration, mo Oral AP/LAI	Inclusion Criteria	Reported Outcome	Age, y (mean ± SD)	% Male	Chronicity	Medication LAI (n)[b] / Oral AP (n)[b]	Medication Dose, mg (mean ± SD)	Key O utcomes
Morritt[69] 1974/UK	33	Single center	Retrospective, dropouts excluded	12/12	SCZ, administered FPZ decanoate and with 1 y record pre/post FPZ depot	# Hps % Hps # Hp days	NR	42.4	NR	FPZ decanoate (33) NR (33)	NR NR	Among 33 patients, the total number of Hp admissions was 60 before FPZ decanoate vs 12 after FPZ decanoate. Total number of days Hp decreased from 2,379 to 801.
Johnson and Freeman[70] 1972/UK	126[y]	Single center	Retrospective, dropouts excluded	12/12	SCZ, administered FPZ depot and with follow-up record of 1 or 2 y	% Hp Hp days	NR	NR	NR	FPZ enanthate or decanoate (126) NR (126)	12.5/5 wk to 25/10 d NR	After 1 y, FPZ was associated with a 57% decrease in Hp admissions and a 48% decrease in length of stay After 2 y, Hp admissions decreased 74%, and length of stay decreased 48%
Denham and Adamson[71] 1971/UK	103	Single center	Retrospective, dropouts excluded	24.8/24.8 (mean)	SCZ, receiving FPZ depot, ≥12-mo follow-up record after injection, with completely documented previous history	# Hps % Hps # Hp days # Hps due to specific reasons # Hp days due to specific reasons	38.5	55.3	Chronic	FPZ (103) NR (103)	FPZ enanthate (6.25–50 mg/ 2 wk) or decanoate (12.5–37.5 mg/ 2 wk) NR	Reduction in Hp admission rate and inpatient time after transition to depot agent
Malm[72] 1971/Denmark	44	Single center	Retrospective, dropouts excluded	36/36	SCZ, chronic, known to have difficulty with adherence to AP oral medication	# Hps # Hp days	NR	100	Chronic	FGA mix (44) NR (44)	NR NR	Lower number of Hps during LAI than during oral AP (rate ratio = 0.294, $P < .0001$)

[a]Original study sample size. [b]Number of patients analyzed. [c]Obtained directly from author. [d]Majority (60.3%) were from 36–55 years old. [e]Based on patients who received at least 4 doses of RLAI (n = 96). [f]Analyzed pre- vs post-LAI phase (6 months each), but study had 18-month extension follow-up phase. [g]Dose at 12 months. [h]Majority (65.2%) were between 25–44 years old. [i]Half of the participants were assessed in a mirror-image setting.

Abbreviations: AE = adverse event, AP = antipsychotic, ARI = aripiprazole, BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, CLO = clozapine, DOI = duration of illness, *DSM-IV = Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, ER = emergency room, FGA = first-generation antipsychotic, FPZ = fluphenazine, GAF = Global Assessment of Functioning, HAL = haloperidol, Hp = hospital/hospitalization, *ICD = International Classification of Diseases*, Int. = international, LAI = long-acting injectable, NR = not reported, PANSS = Positive and Negative Syndrome Scale, OLA = olanzapine, QUE = quetiapine, RIS = risperidone, RLAI = risperidone long-acting injectable, SCZ = schizophrenia, SzAD = schizoaffective disorder, SGA = second-generation antipsychotic, TEAE = treatment-emergent adverse event, UK = United Kingdom, USA = United States of America, VA = Department of Veterans Affairs, ZIP = ziprasidone. Symbol: # = number/number of.

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Supplementary eTable 2. Comparison by Antipsychotic of Number Needed to Harm for Weight Gain ≥ 7%, Somnolence, or Akathisia[a]

	Number Needed to Harm[b]		
Antipsychotic	Weight Gain ≥ 7%	Somnolence Adverse Event	Akathisia Adverse Event
Risperidone	18	13	15
Olanzapine	**6**	**7**	25
Quetiapine IR	**6**	10	ND
Quetiapine XR	22	**7**	188
Ziprasidone	16	15	100
Aripiprazole	20	20	25
Paliperidone	35	42	39
Iloperidone	10	16	ND
Asenapine	35	17	34
Lurasidone	67	11	10
Brexpiprazole	17	50	112
Cariprazine	34	100	15

[a]Updated from Citrome L. *CNS Drugs*. 2013;27:879–911 and Citrome L. *Int J Clin Pract*. 2015;69:978–997.

[b]Number needed to harm values < 10 are bolded in the table. For example, 1 additional outcome of weight gain ≥ 7% is observed every 6 patients treated with olanzapine or quetiapine IR versus placebo; somnolence is observed every 7 patients treated with olanzapine or quetiapine XR versus placebo; and 1 additional patient with complaint of akathisia can be expected every 10 patients treated with lurasidone versus placebo.

Abbreviations: IR = immediate release, ND = no difference from placebo, XR = extended release.

Supplementary eTable 3. Adverse Events (%) Occurring in at Least 5% of Patients Treated With Long-Acting Injectable Antipsychotics (LAIs)[a]

	Risperidone LAI (Risperdal Consta)		Olanzapine Pamoate (Zyprexa Relprevv)			Paliperidone Palmitate LAI (Invega Sustenna)						Paliperidone Palmitate LAI (Invega Trinza)	Aripiprazole LAI (Abilify Maintena)	Aripiprazole Lauroxil (Aristada)		Haloperidol Decanoate (Haldol)
Adverse Event	25 mg	50 mg	405/ 4 wk	210/ 2 wk	300/ 2 wk	39 mg	78 mg	156 mg	234/ 39 mg	234/ 156 mg	234/ 234 mg	273–819 mg	400 (300) mg	441 mg	882 mg	
Gastrointestinal disorders																
Constipation	5	7	…	…	…	…	…	…	…	…	…	…	10	…	…	2
Diarrhea	…	…	2	7	5	0	3	2	1	2	2	…	3	…	…	…
Dry mouth	0	7	2	6	4	3	1	0	1	1	1	…	4	…	…	3.4
Dyspepsia	6	6	…	…	…	…	…	…	…	…	…	…	…	…	…	…
Nausea	3	4	5	5	4	4	4	3	2	2	2	…	—	…	…	…
Vomiting	…	…	6	1	2	5	4	2	3	2	2	…	3	…	…	…
General disorders and administration site conditions																
Fatigue	3	9	4	2	3	1	2	2	1	2	1	…	…	…	…	…
Injection-site reaction	…	…	…	…	…	0	4	6	9	7	10	3	…	…	…	1.2
Injection-site pain	…	…	2	3	2	…	…	…	…	…	…	…	5	3	4	…
Infections and infestations																
Nasopharyngitis	…	…	3	6	1	0	2	2	4	2	2	…	…	…	…	…
Upper respiratory tract infection	2	0	3	1	4	2	2	2	1	2	4	10	4	…	…	…
Investigations																
Weight increased	5	4	5	6	7	4	4	1	1	1	2	9	17	2	2	2.9
Metabolism and nutrition disorders																
Increased appetite	…	…	1	4	6	…	…	…	…	…	…	…	…	…	…	…
Musculoskeletal and connective tissue disorders																
Pain in extremity	6	2	…	…	…	0	2	2	2	3	0	…	…	…	…	…
Back pain	…	…	4	3	5	2	1	3	1	1	1	…	4	…	…	…
Muscle rigidity	…	…	1	4	4	1	<1	<1	1	1	2	…	…	…	…	6.1
Nervous system disorders																
Headache	15	21	13	15	18	11	11	15	11	7	6	9	…	3	5	…
Parkinsonism	8	15	8	14	20	12	10	6	…	…	…	4	…	3	4	7.3
Dizziness	7	11	4	4	1	6	2	4	1	4	2	…	4	…	…	…
Akathisia	4	11	5	11	10	5	6	5	…	5	6	5	11	11	11	3.4
Sedation/somnolence	5	6	13	8	13	5	7	4	1	5	5	…	5	…	…	4.9
Extrapyramidal disorder	…	…	…	…	…	5	2	3	1	0	0	…	…	…	…	13.6
Dyskinesia	…	…	0	2	1	4	6	4	…	…	…	3	…	…	…	<1
Tremor	0	3	3	0	1	…	…	…	…	…	…	…	3	…	…	8
Psychiatric system disorders																
Agitation	…	…	…	…	…	10	5	9	8	5	4	…	…	…	…	…
Anxiety	…	…	…	…	…	8	5	3	5	6	6	…	…	…	…	…
Respiratory, thoracic, and mediastinal disorders																
Cough	4	2	…	5	9	2	3	1	0	1	1	…	…	…	…	…
Nasal congestion	2	0	2	1	7	…	…	…	…	…	…	…	2	…	…	…

[a]These data are derived from product labeling and not from randomized, head-to-head clinical studies comparing LAI antipsychotics. Comparisons must be made with caution, as they reflect different methods of assessment and adverse event definitions across studies.* Rates with placebo, which differ from label to label, are not shown.

*Hamer S, Haddad PM. Adverse effects of antipsychotics as outcome measures. *Br J Psychiatry Suppl.* 2007;191(50):s64–s70.

Symbol: … =event not reported.

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