



Supplementary Material

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

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DOI Number: 10.4088/JCP.13r08440

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Supplementary eTable 1. Detailed Study Characteristics

Study/ Country	n ^{a)}	Data Source	LAI phase	Follow up Duration OAP/LAI (months)	Inclusion Criteria	Reported Outcome	Mean±SD Age (years)	% Male	Chronicity Information	Medication	
										LAI (n) ^{b)}	Mean±SD Dose (mg)
Chang et al. 2012/Taiwan	184	Medical claims data, nationwide	Retrospective, dropouts excluded	12/12	SCZ (ICD-9), started RLAI, followed ≥1Y before and after RLAI initiation, treated regularly with RLAI	# Hp # Outpatient visits # ER visit % Hp ^{c)} Hp days # relapse Cost	36-55 ^{d)}	50.5	DOI ≥6Y in 77.2%	RLAI (184)	total 177/3M
										CLO (7) RIS (80) Other SGA (50) Oral FGA (91)	NR
Rosa et al. 2012/France, Kuwait, Portugal, Saudi Arabia	98	Multinational	Prospective, dropouts excluded	6/6	SCZ/SCZAD (DSM- IV), non-acute, previously treated with OLA (stable dose) and willing to switch to RLAI, not known as RIS non-responder	# experienced Hp # experienced Hp due to psychotic disease # experienced relapse Hp days Psychopathology Social functioning Safety measures	40.2±14.0 ^{e)}	77.1 ^{e)}	Mean DOI: 13.5Y ^{e)}	RLAI (79) ^{f)}	32.6±7.1/2W
										OLA (79) ^{f)}	16.2±5.6
Crivera et al. 2011/US	435	Multicenter	Prospective, dropouts included	12/12 ^{g)}	SCZ(DSM-IV), appropriate for RLAI initiation	# Hp # psychiatric Hp # ER visit % psychiatric Hp	41.9±12.6	66.7	Mean±SD DOI: 17.6± 12.1Y ^{j)}	RLAI (435, 343 ^{g)})	25/2W ^{h)}
										NR (435, 343 ^{g)})	NR
Ren et al. 2011/US	924	VA, multicenter	Retrospective, dropouts included	12/12	SCZ (ICD-9), started RLAI, and had ≥4 RLAI injections	# psychiatric Hp % psychiatric Hp % ≥2 psychiatric Hp Hp days Length of stay	51±11	94	NR	RLAI (924)	38.9±13.0/2W
										NR (924)	NR
Peng et al. 2011/US	147	Commercial claims data, multicenter	Retrospective, dropouts included	6/6	SCZ (ICD-9), started any depot, but without depot injection in the 6M before baseline, ≥2 outpatient visits or ≥1 Hp within 180 days	# Hp % Hp % psychiatric Hp % Hp 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
										NR (147)	NR
Carswell et al. 2010/New Zealand	443	Multicenter (5 centers)	Retrospective, dropouts included	12/12	SCZ (DSM-IV), non- adherent to OAP (or preferred RLAI), intensive treatment in the year prior to switching to RLAI	# Hp Hp days Days of compulsory treatment order Cost	35.9±12.4	64.3	Mean±SD DOI: 11.7± 9.9Y	RLAI (427 ⁱ⁾)	41.5/2W ⁱ⁾
										NR (427 ⁱ⁾)	NR

Study/ Country	n ^{a)}	Data Source	LAI phase	Follow up Duration OAP/LAI (month)	Inclusion Criteria	Reported Outcome	Mean±SD Age (y.o.)	% Male	Chronicity Information	Medication	
										LAI (n) ^{b)}	Mean±SD Dose (mg)
										OAP (n) ^{b)}	
Girardi et al. 2010/Italy	88	Multicenter	Prospective, no dropouts during the 6M phase	6/6 (24) ^{k)}	SCZ/SCZAD (DSM- IV), with clinically inadequate response to ≥2 oral APs within 3M, BPRS-T≥65	% Hp Response rate Psychopathology Safety	41.2±10.6	64.8	Mean±SD DOI: 18±5.0Y Mean±SD # of Hp: 8.26±2.79	RLAI (88) OLA (29) CLO (26) QUE (21) HAL (13) ARI (9) RIS (2)	47.4±10.1/2W NR
Su et al. 2009 ^{l)} /Taiwan	108	Medical claims data, nationwide	Retrospectiv e, dropouts excluded	12/12	SCZ (ICD-9), regularly treated with RLAI for ≥1Y, ≥1Y data in pre- RLAI periods, had <90D hospital stay	# Hp # ER visit HP days # relapse	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 M NR
Lam et al. 2009 ^{m)} /15 countries ⁿ⁾	2300	Multinational	Prospective, dropouts included	12/12	SCZ who participated in RLAI clinical trials	% Hp All cause discontinuation Psychopathology	38.4 ^{o)}	NR	Mean DOI: 10.3Y ^{o)}	RLAI (1748 ^{o)}) OAP (1748 ^{o)})	NR NR
Fuller et al. 2009/US	106	VA (Ohio), multicenter (5 centers)	Retrospectiv e, dropout included	10.2± 6.4/10.2±6.4 (mean±SD)	SCZ/SCZAD (ICD-9) at any time of the study period (1/2003-1/2006), with continuous enrolment throughout the study period, ≥4 injections of RLAI	# psychiatric Hp ^{p)} % psychiatric Hp ^{p)} % ≥2 psychiatric Hp Psychiatric Hp days Psychiatric Hp days/month # psychiatric-related outpatient visits Compliance Cost	51.9±10.2	93	NR	RLAI (106) ARI (7) OLA (19) QUE (30) RIS (57) ZIP (8)	35.5/2W (end) 26.3±4.9 15.1±7.1 423.5±275.5 3.8±1.9 107.7±45.1
Beauchair et al. ^{p)} 2005/Canada	63	Multicenter	Retrospectiv e, dropout included	39.4/ 40.3	SCZ who participated in RLAI clinical trials	# Hp % Hp % experienced ≥2 Hp Hp days All cause discontinuation Concomitant anticholinergic/anxiolytic/ sedative	NR	NR	NR	RLAI (63) NR (63)	NR NR
Bourin et al. 1998/France	48	Single center	Retrospectiv e, dropouts excluded	62.4±33.6/69 .6±38.4 (mean±SD)	SCZ (ICD-10), hospitalized	# Hp Hp days	NR	50	NR	FGA (44) ^{q)} OAP (48)	NR NR

Study/ Country	n ^{a)}	Data Source	LAI phase	Follow up Duration OAP/LAI (months)	Inclusion Criteria	Reported Outcome	Mean±SD Age (years)	% Male	Chronicity Information	Medication	
										LAI (n) ^{b)}	Mean±SD Dose (mg)
										OAP (n) ^{b)}	
Svestka et al. 1984/Czech	34	Single center	Prospective, dropouts included	10.3/10.3	SCZ, in remission	% Hp	37.4	23.5	Mean DOI: 9.2Y # Hps in lifetime (range): 1-12	clopenthixol decanoate (34)	169.5/3.7W
										NR	NR
Waldmann et al. 1984/Germany	65	Single center	Retrospectiv e, dropouts excluded	31.2/31.2	SCZ/SCZAD, outpatients and patients in day hospital who were receiving FPZ decanoate	# Hp	NR	27.7	Duration of treatment: 1- 9Y	FPZ (65)	17.7/3W
										NR (65)	NR
Michel et al. 1981/Chile	112	Single center	Retrospectiv e, dropouts excluded	12-17/12-17 (range)	SCZ, on depot when study was conducted	Hp days	25-44 ^{r)}	67.9	NR	FPZ	NR
										NR	NR
Tan et al. 1981/Singapore	127	Multicenter (6 centers)	Retrospectiv e, dropouts excluded	24/24	SCZ, duration of illness ≤8Y, ≥24M treatment before and after the institution of FPZ depot	# Hp Hp days Compliance	32.5±8.8	61.4	6-8 ^{s)}	FPZ (127)	25/M ^{t)}
										NR (127)	NR
Arato 1979/Hungary	51	Single center	Retrospectiv e, dropouts excluded	44/26	SCZ/SCZAD, ≥1Y on depot, ≥2 Hp in the past	# Hp Number of patients who experienced Hp	34	100	Mean DOI: 7.2Y	Mixed FGA	FPZ (12.5-25 mg/4W) ^{u)} , flupenthixol 20mg/3W) ^{u)}
										NR	NR
Devito et al. 1978/USA	122 ^{v)}	Single center	Retrospectiv e, dropouts excluded	12/12	SCZ spectrum disorders, treated in the same inpatient program and referred for outpatient treatment in the FPZ program	# Hp % Hp Length of stay # Hp per patient	18-39 ^{w)}	50.8	NR	FPZ (61 ^{v)})	37.5mg/3-4W
										NR (61 ^{v)})	NR
Polonowita and James 1976/New Zealand	43	Single center	Retrospectiv e, dropouts included	13/13	SCZ (ICD-8), started FPZ depot.	# Hp Hp days	NR	67.4	NR	FPZ decanoate (43)	NR
										NR (43)	NR
Lindholm 1975/Sweden	24	Multicenter (2 centers)	Retrospectiv e, dropouts excluded	26.9/26.9	SCZ, administered perphenazine enanthate for >1Y	# Hp % Hp Hp days Concomitant antiparkinson medication	44.9	25.0	Mean DOI: 6.8Y	perphenazine enanthate (24)	107 mg
										NR (24)	NR

Study/ Country	n ^{a)}	Data Source	LAI phase	Follow up Duration OAP/LAI (months)	Inclusion Criteria	Reported Outcome	Mean±SD Age (years)	% Male	Chronicity Information	Medication	
										LAI (n) ^{b)} OAP (n) ^{b)}	Mean±SD Dose (mg)
Gottfries and Green 1974/Sweden	58	Single center	Retrospective, dropouts excluded	NR ^{x)}	SCZ, discharged, treated with flupenthixol decanoate during observational period	# relapse requiring Hp % Hp Hp days Length of stay All cause discontinuation	NR	NR	Patients started LAI during Hp and later were transferred to ambulant treatment.	flupenthixol decanoate (58)	40/2W as a general rule, range (20mg- 60mg)
Morritt 1974/UK	33	Single center	Retrospective, dropouts excluded	12/12	SCZ, administered FPZ decanoate and with 1 year record pre/post FPZ depot	# Hp % Hp Hp days	NR	42.4	NR	FPZ decanoate (33)	NR
Johnson and Freeman 1972/UK	126 ^{y)}	Single center	Retrospective, dropouts excluded	12/12 ^{y)}	SCZ, administered FPZ depot and with follow- up record of 1 or 2Y ^{y)}	% Hp Hp Days	NR	NR	NR	FPZ enanthate or decanoate (126 ^{y)})	12.5/5W – 25/10D
Denham and Adamson 1971/UK	103	Single center	Retrospective, dropouts excluded	24.8/24.8 (mean)	SCZ, receiving FPZ depot, ≥12M follow-up record after injection, with completely documented previous history	# Hp % Hp Hp days # Hp due to specific reasons Hp days due to specific reasons	38.5	55.3	Chronic	FPZ (103)	FPZ enantate (6.25-50 mg/2W) or decanoate (12.5-37.5 mg/2W)
Malm 1971/Denmark	44	Single center	Retrospective, dropouts excluded	36/36	SCZ, chronic, known to have difficulty with adherence to AP oral medication	# Hp Hp days	NR	100	Chronic	FGA mix (44)	NR

a) Original study sample size

b) Number of patients analyzed

c) Obtained directly from author

d) Majority (60.3%) were between 36-55 years old

e) Based on patients who received at least 4 doses of RLAI (n=96)

f) Patients who received efficacy assessments and completed 6M of treatment were included in analysis.

g) Analysis for hospitalization risk was conducted on subpopulation who received >2 RLAI injections with 12M observation.

h) Majority (73.8%) started with a dose of 25mg/2W

i) Patients who were transferred to other health services, died, or spent more than 12 months as an inpatient were excluded from the analysis.

j) Dose at 12M

k) Analyzed pre- vs. post-LAI phase (6M each), but study had 18M extension follow up phase.

l) Only hospital days was used for the analysis due to the patient overlap with Chang et al.

m) Unpublished data

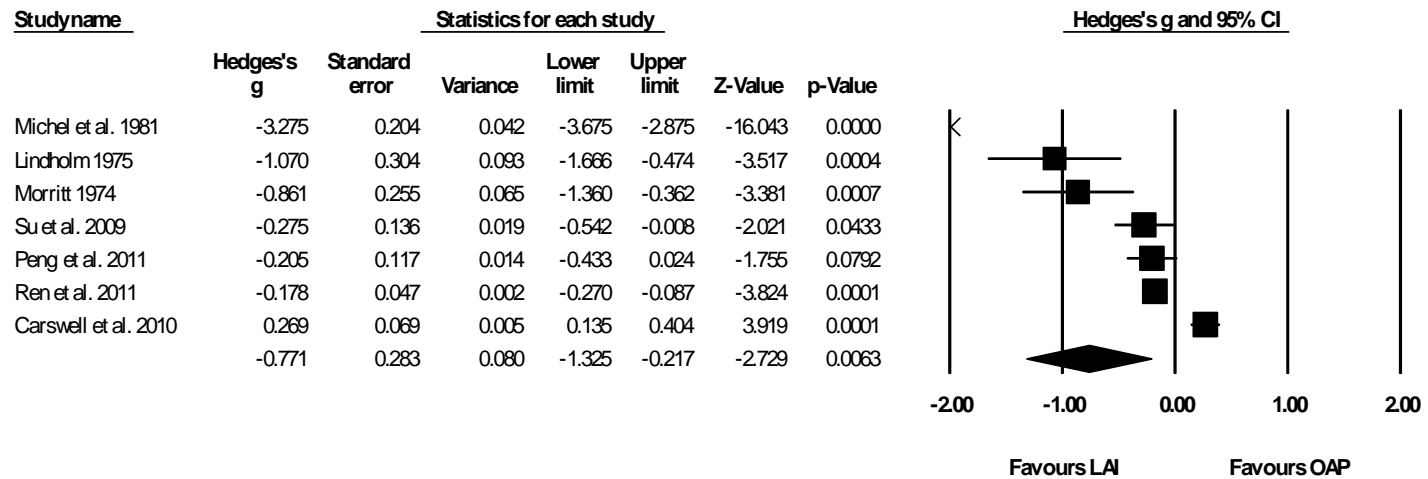
n) Australia, Belgium, Brazil, Canada, Czech, Denmark, Greece, Korea, Mexico, Netherland, Norway, Russia, Slovakia, Spain and Sweden

- o) Analyzed 1748 patients who were taking oral atypical antipsychotics before RLAI
- p) Not analyzed due to potential overlap with Ren et al.
- q) 44 patients were analyzed in LAI phase.
- r) Majority (65.2%) were between 25-44 years old.
- s) Illness durations was 6-8Y for the majority (65.3%) of patients
- t) Dose for majority of the patients (96.1%)
- u) Doses for majority of the patients
- v) Majority (57.4%) were between 18-39 years old.
- w) Half of the participants were assessed in a mirror-image setting.
- x) Mean±SD observation period for 36 patients who had relapse(s) was 43.2(10.8) months.
- y) Patients with 1 year of follow up period were analyzed in this meta-analysis.

Abbreviations: AP=antipsychotic, ARI=aripiprazole, BPRS-T=brief psychiatric rating scale, CLO=clozapine, D=days, DOI=duration of illness, DSM-IV=Diagnostic and Statistical Manual of Mental Disorders - fourth edition, ER=emergency room, FGA=first generation antipsychotic, FPZ=fluphenazine, HAL=haloperidol, Hp=hospital, hospitalization, ICD=International Classification of Diseases, LAI=long acting injectable, M=months, NR=not reported, OAP=oral antipsychotic, OLA=planzapine, QUE=quetiapine, RIS=risperidone, RLAI=risperidone long acting injection, SCZ=schizophrenia, SCZAD=schizoaffective disorder, SGA=second generation antipsychotic, VA=Veterans Affairs, W=week, Y=year, ZIP=ziprasidone

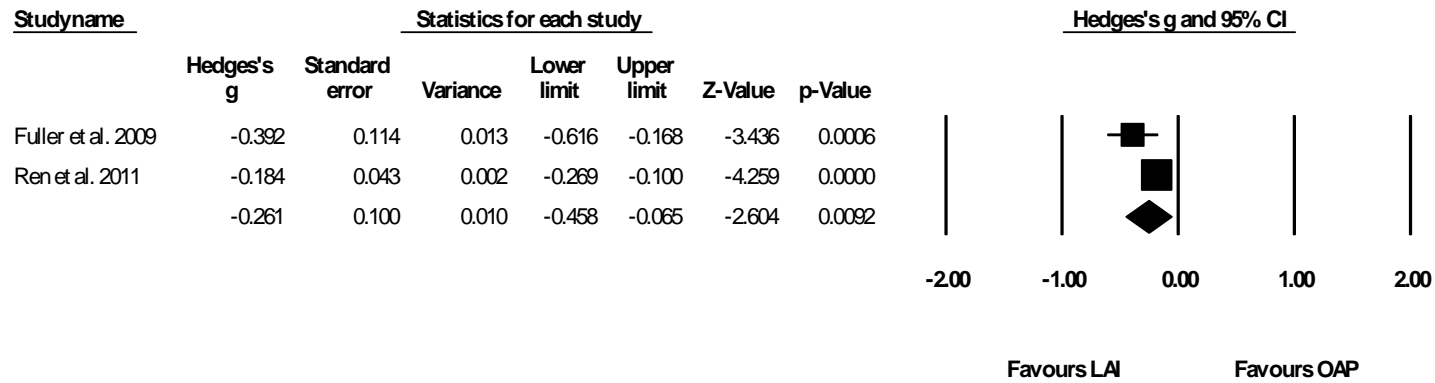
Supplementary eFigure 1. Hospitalization Days

Hospitalization Days

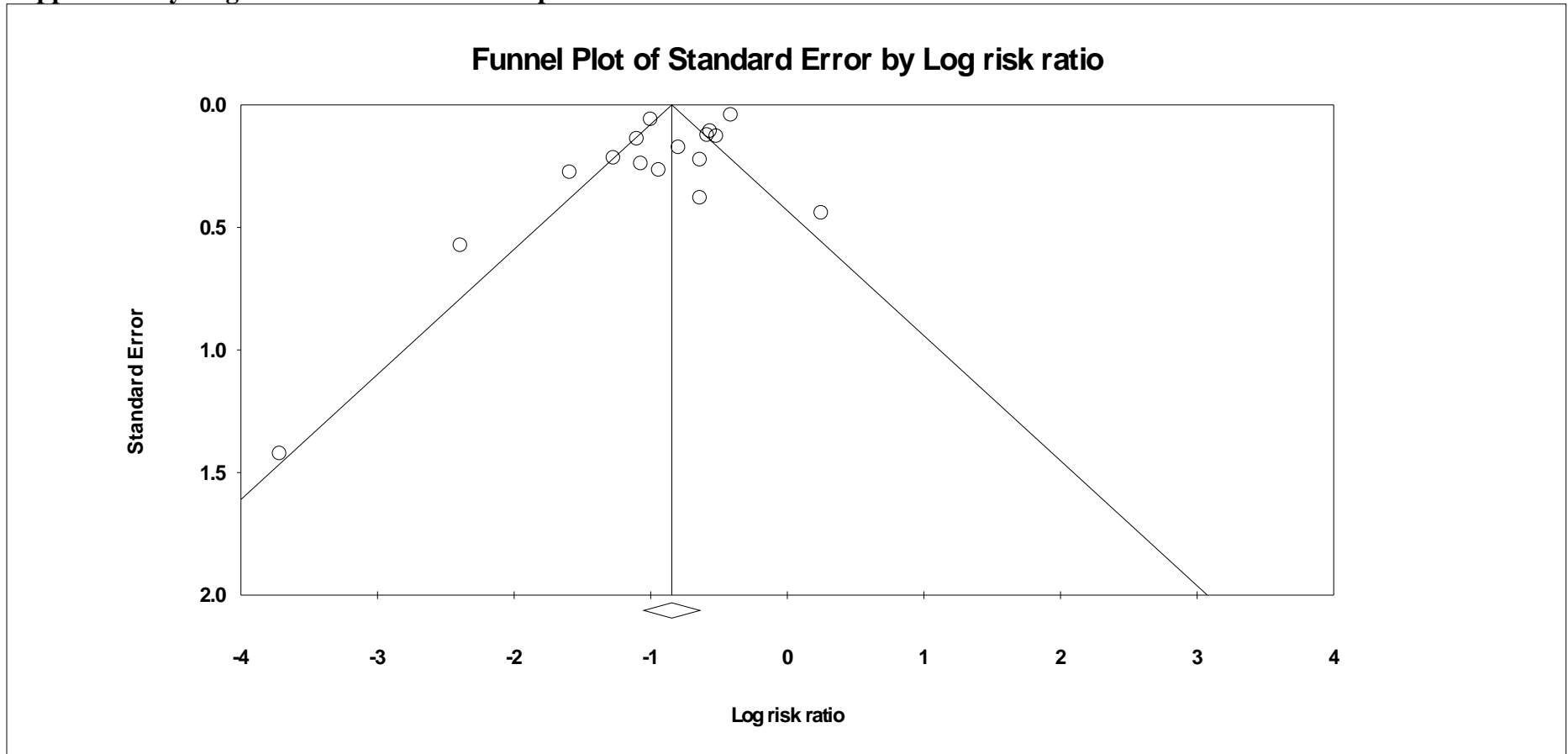


Supplementary eFigure 2. Length of Stay

Length of Stay



Supplementary eFigure 3. Funnel Plot for Hospitalization Risk



Supplementary eFigure 4. Funnel Plot for Number of Hospitalization

