Potential Benefit of Digital Pill from Psychiatrist's Perspective

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Financial Disclosure

- **Consultant Fee**
  - Dainippon-Sumitomo, Meiji, Novartis, Otsuka, Taisho
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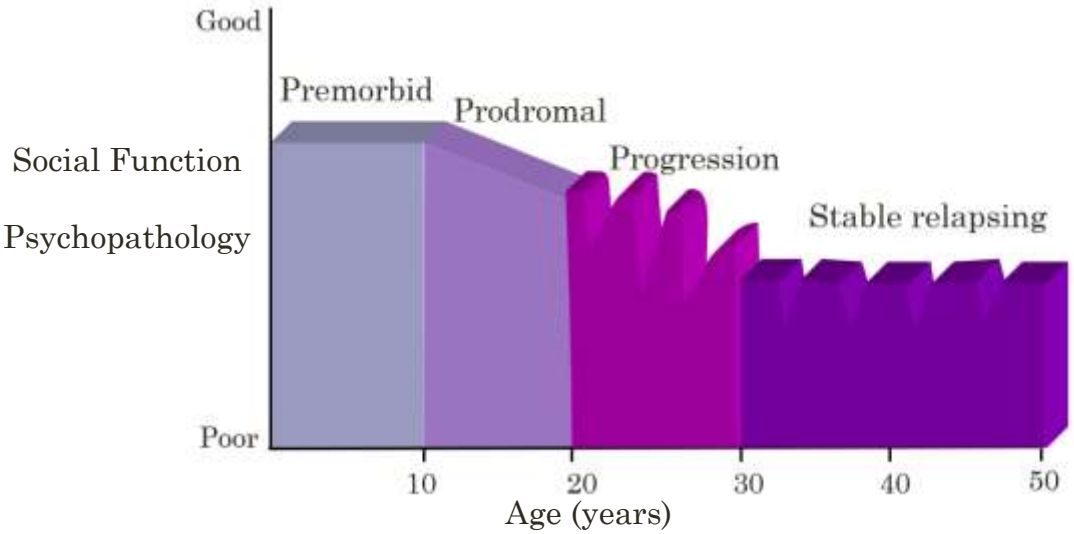
Long Term Prognosis of Schizophrenia

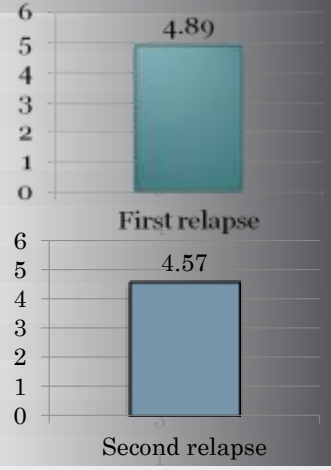


Lieberman, J.A. : Journal of Clinical Psychiatry, 57 (S.11), 68-71, 1996

Cumulative Relapse Rate after First Episode in Schizophrenia

Year from the Previous Episode	Relapse Rate [95%CI]
	1st Relapse – 104 Pts at Risk
1	16.2 [8.9-23.4]
2	53.7 [43.4-64.0]
3	63.1 [52.7-73.4]
4	74.7 [64.2-85.2]
5	81.9 [70.6-93.2]
	2nd Relapse – 63 Pts at Risk
1	19.1 [8.4-29.9]
2	48.7 [33.6-63.9]
3	56.0 [43.2-80.2]
4	56.0 [43.2-80.2]
5	78.0 [46.5-100.0]

Risk of relapse when NOT taking medication



Robinson D, et al. Arch Gen Psychiatry 1999;56:241–7

Antipsychotic Continuation vs. Placebo Meta-analysis

	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)

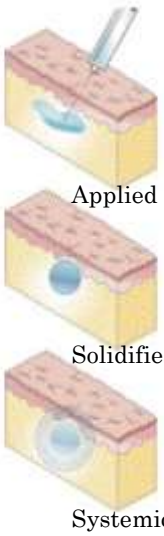
Leucht et al. Lancet 2012

Non/poor adherence in Schizophrenia

Country, Population	Number of Patients	Measurement Method	Non-/poor Adherence
Schizophrenia, Norway (Jónsdóttir H et al. 2010)	280	Serum concentration	58.4%
Schizophrenia, USA (Dibonaventura M et al. 2012)	876	Self-report	48.4%
Schizophrenia, Nigeria (Adelufosi AO 2012)	313	Self-report	40.3%
Schizophrenia, USA Medicaid beneficiaries (Gilmer TP et al. 2004)	2,801	Pharmacy Records	40%
Schizophrenia, USA VA (Valenstein M et al. 2004)	63,214	Pharmacy Records	40%
Schizophrenia, first episode (Perkins DO et al. 2008)	400	Discontinuation against medical advice	37.1% (K-M curve) 28.8% (raw)
Schizophrenia, USA VA (Valenstein M 2006)	34,128	Pharmacy Records	36.0-37.1%
Schizophrenia, France (Dassa D et al. 2010)	291	Self-report	30.0%

Kane, Kishimoto and Correll. World psychiatry 2013

Long Acting Injectable Antipsychotics Minimise Therapy Disruptions



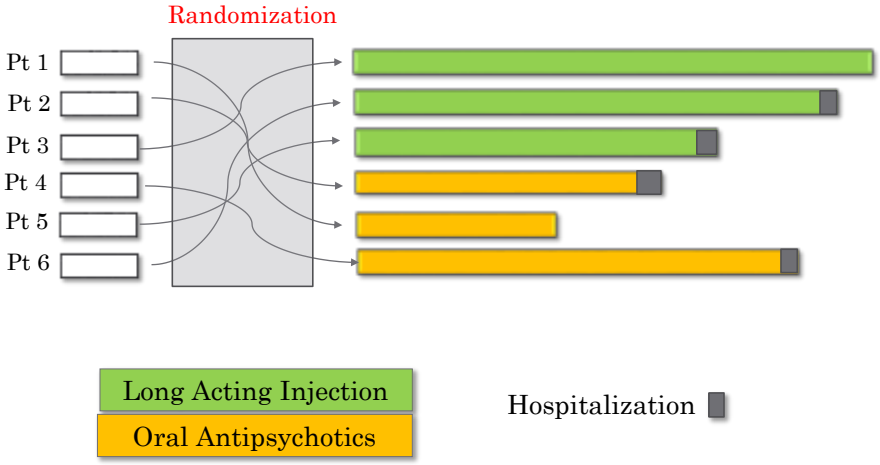
- Assure medication delivery
- Immediate awareness of non-adherence
- No abrupt loss of efficacy if dose missed
- Freedom from daily medication
- etc.

- Needle pain
- Possible emergence of injection site side effects
- Impossible to discontinue/reduce dosage immediately
- etc.

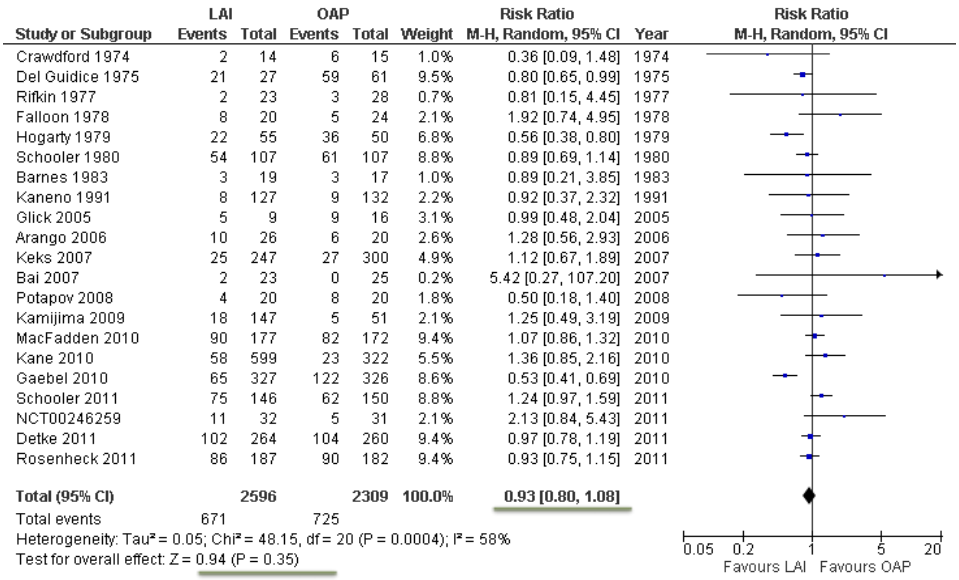
Need for Good Evidence on Comparative Effectiveness of Long Acting Injectable (LAIs) vs. Oral Antipsychotics (OAPs)

- Conducted series of meta-analyses comparing LAIs and OAPs
- Examined various data sets including RCT data as well as other data sets derived from real world clinical practice

Randomized Controlled Study



Relapse Rate in Randomized Controlled Studies (Long Acting Injectable vs. Oral Antipsychotics)

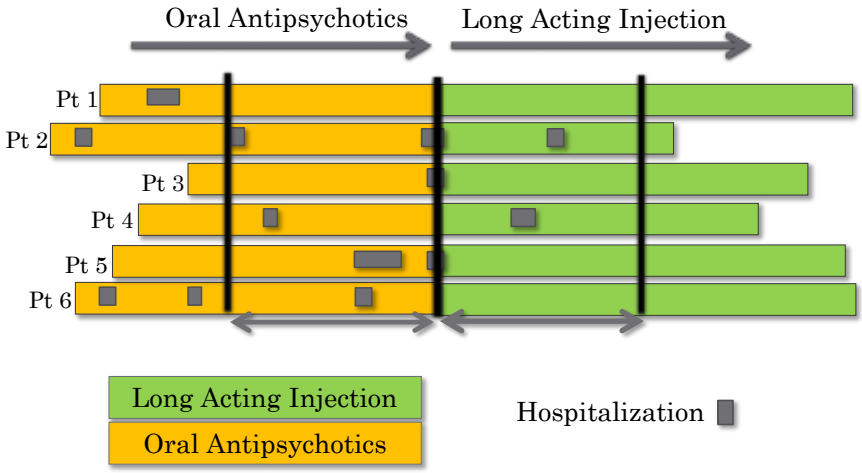


Study or Subgroup	LAI Events	LAI Total	OAP Events	OAP Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Crawdford 1974	2	14	6	15	1.0%	0.36 [0.09, 1.48]	1974
Del Guidice 1975	21	27	59	61	9.5%	0.80 [0.65, 0.99]	1975
Rifkin 1977	2	23	3	28	0.7%	0.81 [0.15, 4.45]	1977
Falloon 1978	8	20	5	24	2.1%	1.92 [0.74, 4.95]	1978
Hogarty 1979	22	55	36	50	6.8%	0.56 [0.38, 0.80]	1979
Schooler 1980	54	107	61	107	8.8%	0.89 [0.69, 1.14]	1980
Barnes 1983	3	19	3	17	1.0%	0.89 [0.21, 3.85]	1983
Kaneno 1991	8	127	9	132	2.2%	0.92 [0.37, 2.32]	1991
Glick 2005	5	9	9	16	3.1%	0.99 [0.48, 2.04]	2005
Arango 2006	10	26	6	20	2.6%	1.28 [0.56, 2.93]	2006
Keks 2007	25	247	27	300	4.9%	1.12 [0.67, 1.89]	2007
Bai 2007	2	23	0	25	0.2%	5.42 [0.27, 107.20]	2007
Potapov 2008	4	20	8	20	1.8%	0.50 [0.18, 1.40]	2008
Kamijima 2009	18	147	5	51	2.1%	1.25 [0.49, 3.19]	2009
MacFadden 2010	90	177	82	172	9.4%	1.07 [0.86, 1.32]	2010
Kane 2010	58	599	23	322	5.5%	1.36 [0.85, 2.16]	2010
Gaebel 2010	65	327	122	326	8.6%	0.53 [0.41, 0.69]	2010
Schooler 2011	75	146	62	150	8.8%	1.24 [0.97, 1.59]	2011
NCT00246259	11	32	5	31	2.1%	2.13 [0.84, 5.43]	2011
Detke 2011	102	264	104	260	9.4%	0.97 [0.78, 1.19]	2011
Rosenheck 2011	86	187	90	182	9.4%	0.93 [0.75, 1.15]	2011
Total (95% CI)		**2596**		**2309**	**100.0%**	**0.93 [0.80, 1.08]**	
Total events	671		725				

Heterogeneity: Tau² = 0.05; Chi² = 48.15, df = 20 (P = 0.0004); I² = 58%
Test for overall effect: Z = 0.94 (P = 0.35)

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

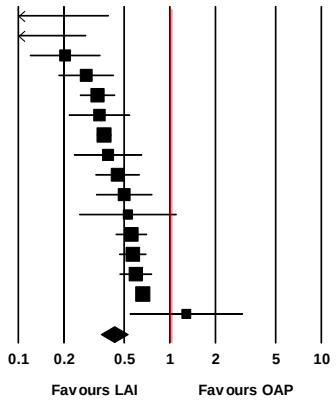
Mirror-Image Study



Mirror-image study compares what happens before and after the introduction of a new treatment, using equal intervals.
Each patient serve as his/her own control.

Relapse Rate in Mirror Image Studies (Long Acting Injectable vs. Oral Antipsychotics)

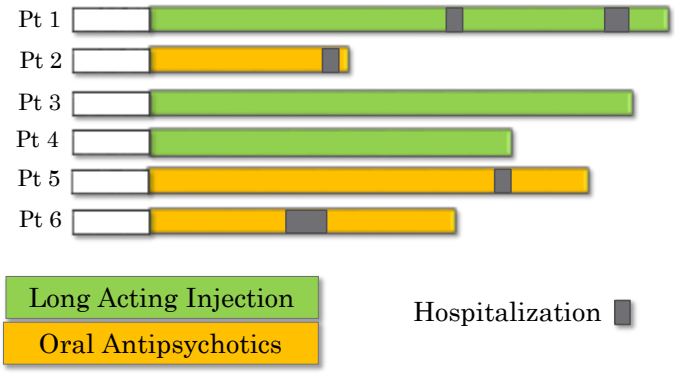
Study name	Outcome	Statistics for each study				
		Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Girardi et al. 2010	Hospitalization Risk	0.024	0.001	0.397	-2.609	0.0091
Beauclair et al. 2005	Hospitalization Risk	0.092	0.030	0.282	-4.166	0.0000
Arato & Erdos 1979	Hospitalization Risk	0.204	0.119	0.350	-5.761	0.0000
Devito et al. 1978	Hospitalization Risk	0.281	0.183	0.430	-5.844	0.0000
Denham & Adamson 1971	Hospitalization Risk	0.333	0.254	0.438	-7.884	0.0000
Morritt 1974	Hospitalization Risk	0.343	0.214	0.550	-4.440	0.0000
Lam et al. 2009	Hospitalization Risk	0.369	0.327	0.415	-16.569	0.0000
Lindholm 1975	Hospitalization Risk	0.391	0.232	0.660	-3.515	0.0004
Peng et al. 2011	Hospitalization Risk	0.452	0.321	0.636	-4.554	0.0000
Gottfries & Green 1974	Hospitalization Risk	0.500	0.324	0.771	-3.136	0.0017
Rosa et al. 2012	Hospitalization Risk	0.529	0.251	1.116	-1.672	0.0944
Chang et al. 2012	Hospitalization Risk	0.557	0.437	0.711	-4.697	0.0000
Johnson & Freeman 1972	Hospitalization Risk	0.570	0.461	0.704	-5.203	0.0000
Crivera et al. 2011	Hospitalization Risk	0.597	0.463	0.768	-4.003	0.0001
Ren et al. 2011	Hospitalization Risk	0.663	0.611	0.720	-9.746	0.0000
Svestka et al. 1984	Hospitalization Risk	1.286	0.541	3.056	0.569	0.5694
		0.428	0.349	0.525	-8.113	0.0000



16 studies, 4066 patients
Risk Ratio=0.43, 95%CI:0.35-0.53, p<0.0001
NNT=3

Kishimoto et al. Journal of Clinical Psychiatry 2013

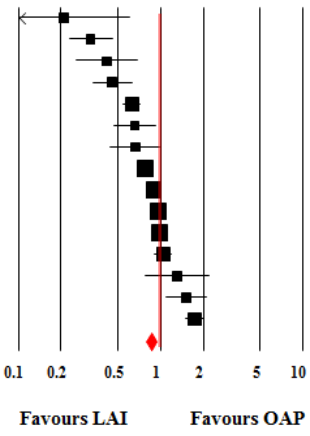
Cohort Study



Longitudinal follow up of patients who initiated new treatment.
No randomization; LAI patients can be severer than OAP patients.

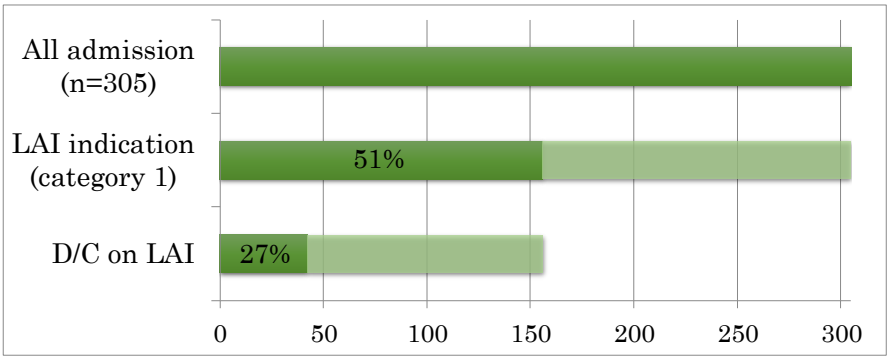
Relapse Rate in Cohort Studies (Long Acting Injectable vs. Oral Antipsychotics)

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



Kishimoto et al. Schizophrenia Bull 2017

% LAI indication and % D/C on LAI Chart Review Study

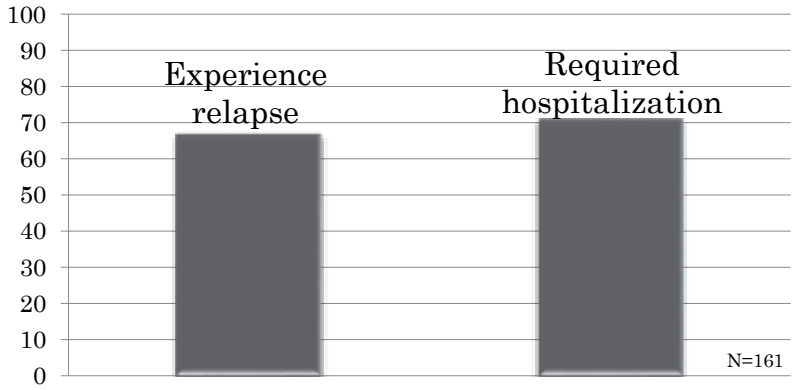


LAI indication (category 1): a) Index hospitalization due to non-adherence OR b) partial-adherence before index hospitalization AND ≥1 past hospitalization due to non-adherence

Kishimoto T, et al. Int Clin Psychopharmacol. 2017 May;32(3):161-8.

Prescribers' Recognition of Patients' Adherence Survey Study

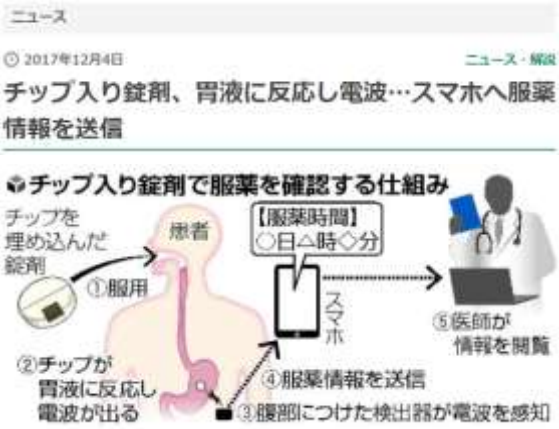
Q: Estimate the poor/non-adherence rate of your patients when they …



Kishimoto et al. In preparation

Potential Role of Digital Medicine

- Reminder to assist patients to take their medication
- Utilize other information (activity/sleep patterns etc.) for precision medicine
- Identify who needs more help to take their medication
- Information for the next treatment strategy



精神疾患の治療に使う錠剤に電波を発するチップを埋め込み、患者本人や主治医らが服薬を確認できるシステムを、大塚製薬（東京）が開発した。同社によると、こうしたシステムは世界初。薬の飲み忘れを防ぐ新手法として期待される。

抗精神病薬「エビリファイ」とチップを組み合わせた製剤などについて、米食品医薬品局から先月承認を得た。日本国内の販売は未定という。

錠剤を飲むと３ミリ四方のチップが胃液に反応して電波を発し、腹部に貼った検出器が感知する。服薬情報はスマートフォンに送信され、患者はアプリで服用した日時が分かる。チップは便とともに排出される。

統合失調症などの精神疾患の患者は薬の服用を中断することが多い。システムには、患者の同意を得て服薬情報を医師がパソコンで閲覧できる機能があり、診療や服薬指導に生かせる。

岸本泰士郎・慶応大学専任講師（精神科）の話「服薬状況がシステムで明確になれば、薬の効果が出ない時に次の治療法を患者に示しやすくなる。ただ、チップの仕組みや目的を患者が十分理解して使うことが大切で、米国での使用状況に注目したい」

2017年12月4日 読売新聞

Thank you very much for your attention

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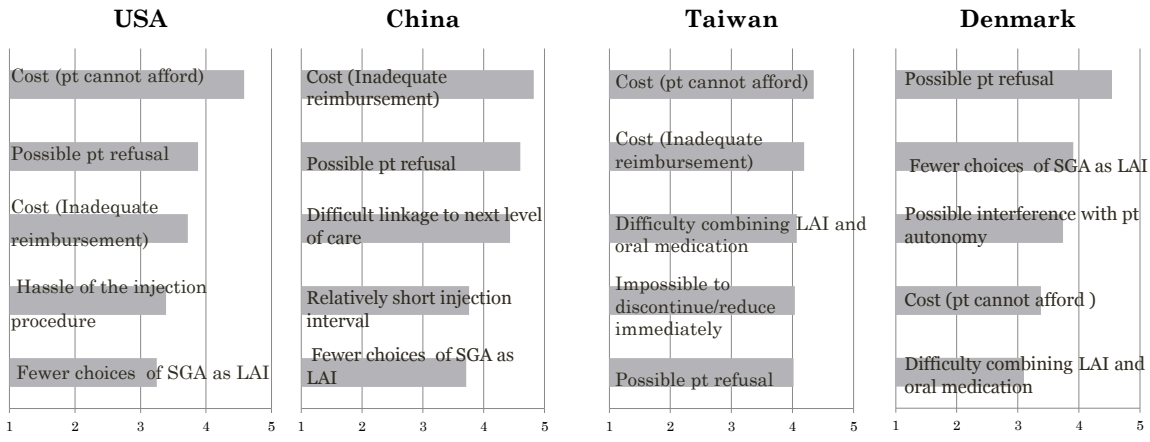
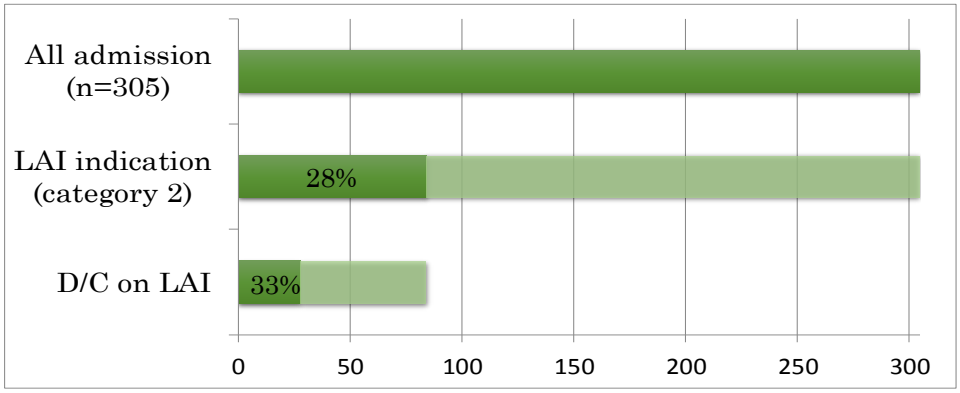
Barriers to prescribe LAI Survey Study



Kishimoto et al. In preparation, Preliminary Data

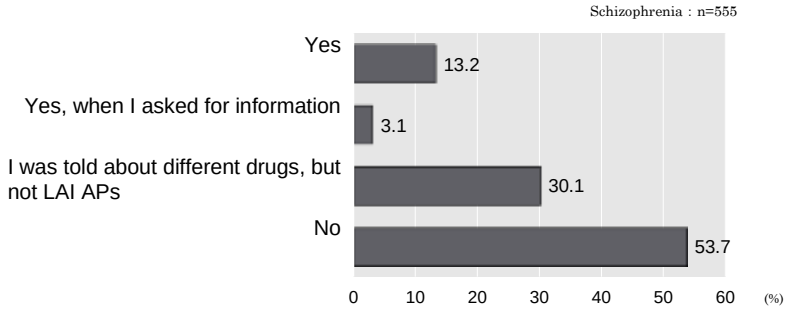
% LAI indication and % D/C on LAI Chart Review Study



LAI indication (category 2) : Index hospitalization due to non-adherence AND ≥1 past hospitalization due to non-adherence

Kishimoto T, et al. Int Clin Psychopharmacol. 2017 May;32(3):161-8.

Has your doctor ever told you about LAI antipsychotics?

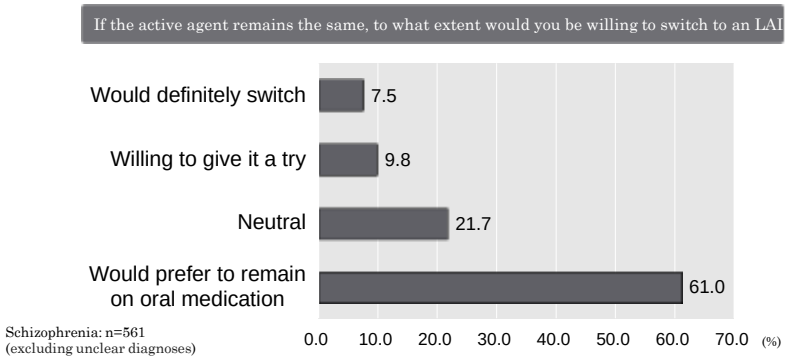


Mental health service user survey of 1,000 people – NPO Corporation National Mental Disabilities Network Council 2014 Survey

AP, antipsychotic; LAI, long-acting injectable

NPO Corporation National Mental Disabilities Network Council: The latest statistics on drug prescription for schizophrenia and depression – 2014 edition, P18, NPO Corporation, 2014.

Switching from oral to LAI antipsychotics



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AP, antipsychotic; LAI, long-acting injectable

NPO Corporation National Mental Disabilities Network Council: The latest statistics on drug prescription for schizophrenia and depression – 2014 edition, P19, NPO Corporation, 2014.

Evidence： Randomized Controlled Studies

無作為化比較試験におけるエビデンス