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Review article

Long-acting injectable antipsychotics in patients with schizophrenia: systematic review and mixed treatment meta-analysis

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Long-acting injectable antipsychotics (LAIs) are recommended for schizophrenic patients who cannot adhere to oral medication. We systematically reviewed randomized controlled trials of 6 LAIs available in Thailand including fluphenazine, flupentixol, haloperidol, zuclopenthixol, paliperidone, and risperidone in PubMed/MEDLINE and the Cochrane library (1955–Nov 2013). Inclusion was limited to studies of schizophrenia ≥24 weeks duration published in English. We selected 17 of 1,245 articles including 1,904 patients. The number of patients ranged from 19 to 747 per study (median 54). Mean study duration was 52.3 weeks (24–96 weeks) and median quality score using a Jadad scoring method was 4 (2–5). We applied a Bayesian model with a mixed treatment comparison approach for 3 competing risk outcomes including relapse, and discontinuation because of adverse events or other reasons. Based on the random effect model preferred by a goodness of fit analysis, risperidone had the lowest 52 week probability of relapse (mean ± SD, 0.26 ± 0.321) followed by paliperidone (0.30 ± 0.314). Zuclopenthixol had the lowest probability of discontinuation because of an adverse event (0.07 ± 0.159) or other reasons (0.26 ± 0.295). Risperidone had the highest probability of preventing relapse (0.35 ± 0.476) or discontinuation for other reasons (0.31 ± 0.461). Zuclopenthixol had the highest probability of preventing discontinuation because of adverse effects (0.31 ± 0.464). All 6 LAIs tended to have a lower risk of relapse compared with placebo. Differences between LAIs preventing any treatment discontinuation or relapse were seen, but limited in our analysis.

Keywords: Competing risk outcomes, long acting injectable antipsychotics, meta-analysis, mixed treatment comparison

Schizophrenia is used to describe a major psychiatric disorder of an individual's perception, thoughts, affect, and behavior. Schizophrenia is a chronic psychiatric disease, which includes hallucinations, delusions, thought disorder, disorganized speech, grossly disorganized behavior, reduced motivation, and reduced social functioning [1]. Worldwide, schizophrenia is estimated to be a top ten illness with respect to disability [2]. A systematic review of prevalence showed the median lifetime prevalence of the condition was 3.3 per 1,000 persons [3]. The Mental Disorders in Thailand report 2004 showed the recognized prevalence of schizophrenia was 0.47% for men and 0.38% for women, while the annual incidence was 0.021% for men and 0.015% for women [4]. Years of lives with disability for schizophrenia were ranked as the 3rd and 5th in women and men respectively in 2007 [4]. More recently, a study in Thailand presented the prevalence of schizophrenia with ages of 15–59 years was 8.8 per 1,000 persons with a male-to-female ratio of 1.1-to-1 [5].

The ultimate goal of the treatment of schizophrenia is to enable patients to lead maximally productive and meaningful lives. Because there is

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no definitive cure, healthcare providers should have plans to include treatment interventions directed towards decreasing manifestations of the illness, rehabilitative services directed towards enhancing adaptive skills, and social support mobilization aimed at optimizing function and quality of life [6]. To date, antipsychotic medications are the primary treatment for schizophrenia in both hospital and community settings. Efficacy of antipsychotics in the management of acute psychotic episodes and relapse prevention have been discussed and established [7]. Conventional or first generation antipsychotic agents are effective, but are associated with numerous and often severe side effects including sedation, weight gain, sexual dysfunction, movement disorders, extra pyramidal side effects, parkinsonism, akathisia, dystonia, and tardive dyskinesia [8]. Newer or second-generation antipsychotics were introduced to overcome the limitations of this prior group. They are associated with less movement disorders, but are more likely to result in weight gain and metabolic syndromes, both contributing to the risk of type 2 diabetes and cardiovascular disease [9]. In addition, raising the level of serum prolactin is another concern for patients taking antipsychotics [10].

Oral antipsychotic medication was introduced as a first line pharmacological treatment for patients with newly diagnosed schizophrenia [1]. To promote recovery, it is suggested that patients remain on long-term maintenance unless contraindication arises. Long-acting antipsychotic injections (LAIs) could be offered to patients who either prefer such treatment after an acute episode or who need to avoid nonadherence (either intentional or unintentional) to antipsychotic medication. Thai guidelines for schizophrenia treatment in 2001 indicate LAIs are chosen for patients with oral nonadherence [11]. Under controlled study conditions, up to 25% of patients are noncompliant within 7–10 days. When patients were monitored for longer, at least 50% became partially complaint or noncompliant within 1 year, and 75% within 2 years of discharge [12, 13]. Although most patients responded well to oral antipsychotic medication, the discontinuation rate within 18 months was as high as 74% [14]. Long-term adherence to medication is one of the most challenging issues in the treatment of schizophrenia [15]. Patients may discontinue medication because of lacking of efficacy, intolerable adverse events or other reasons. As a consequence, most patients suffer frequent symptom relapses, which may ultimately result in rehospitalization [16].

The CATIE study aimed to prospectively measure the effectiveness of oral antipsychotic treatment by assessing the final number of patient participants who remained on their treatment until the end or the study [14]. With this, the U.K. National Institute of Health and Clinical Excellence (NICE) proposed a model to include three competing risk outcomes; number of patients relapsed, discontinuation because of intolerance adverse events, and discontinuation because of other reasons [1].

Several LAIs are registered in Thailand, including fluphenazine decanoate (fluphenazine), flupenthixol flupentixol decanoate (flupentixol), haloperidol decanoate (haloperidol), zuclopenthixol decanoate (zuclopenthixol), paliperidone palmitate (paliperidone), and risperidone LAI (risperidone). Currently, no direct evidence associated with the comparability of the efficacy of the 6 LAIs has been published. Those data are necessary not only for supporting the healthcare profession's product selection for their patients, but also for supporting their cost effectiveness analysis. When there are many treatments available, but they have not been compared in a head-to-head manner, systematic reviews and mixed treatment comparison meta-analysis can be used to compare multiple products [17-19]. This approach is particularly useful when there are numerous studies of similar groups of patients and outcomes. Competing risk outcomes in relapse prevention with antipsychotics in patients with schizophrenia have been applied in health economic evaluation by the NICE guidelines on core interventions in the treatment and management of schizophrenia 2009 [1, 20]. Competing risk meta-analysis permits studies with different follow up times, multiple outcomes, and multiple treatments to be compared in a single analysis setting [20].

The primary objective of this study was to compare three competing risk outcomes of multiple LAIs antipsychotics available in Thailand for subjects with schizophrenia by using mixed treatment comparison meta-analysis. Three competing risk outcomes were number of relapses, discontinuation because of intolerable adverse events, and discontinuation because of other reasons. Systematic review of randomized controlled trials (RCT) was applied. The outcome of this study was planned to support our economic evaluation of LAIs at the next stage.

Method

Search

We conducted a search strategy using PubMed/MEDLINE and the Cochrane library (1955–November 2013), for randomized controlled trials (RCTs) of LAIs in schizophrenia. Search terms included: (1) antipsychotics, (2) schizophrenia, (3) randomized controlled trials, and (4) long acting injection (depot). A manual search was also used if there were relevant references. Our search was limited to English full publications only.

Inclusion criteria

Studies were eligible for inclusion if they involved fluphenazine, flupentixol, haloperidol, zuclopenthixol, paliperidone, and/or risperidone, a RCT study design, had a placebo comparison group, and evaluated patients with schizophrenia who were 18 years old or older. The study duration had to be 24 weeks or longer and studies needed to provide data regarding symptom control outcomes, discontinuation, relapses or rehospitalization. We excluded LAIs that were not registered in Thailand before November 2013.

Data extraction and outcomes

Three investigators (ON, CR, and MP) conducted the review and data extraction. Any lack of consensus was discussed and resolved. The primary binary outcome was all-cause discontinuation including 1 relapse (defined as relapse or discontinuation because of inefficacy), 2 discontinuation because of intolerable adverse events, and 3 discontinuation because of other reasons (such as nonadherence). These outcomes were treated as competing risks meaning that within the study time frame, patients who were under treatment and in remission (which would be considered a successfully treated case) were at risk of either one of three outcomes.

Data analysis

Intent-to-treat analysis, was evaluated where patient participants who dropped out since arm assignment, were included in the study. Study quality was evaluated using the scoring system developed by Jadad and colleagues. This quality tool assess the likelihood of systematic errors, based on the description of randomization technique, allocation concealment, blinding method, and participant withdrawal description [21]. Although the data regarding mutually exclusive end-points may be presented either in the form of hazard ratio statistics or in form of cumulative count statistics, hazard ratio statistics account for censoring and incorporate times to events that were different among the included studies. We assumed constant hazards over the period of observation of each study to meet the assumption of proportional hazards for each outcome. The hazard and precision for each point on placebo was estimated from a model of studies where placebo was a comparator in order to estimate the treatment effect relative to placebo on the log-hazard scale.

Statistical analysis

Mixed treatment comparisons for the competing risks logistic regression models using a Bayesian framework was applied. Data were analyzed by using WingBUGS software (version 1.4.3, MRC Biostatistics Unit, Cambridge, England) to derive 52 week probabilities with standard deviations (SDs), hazard ratios (HRs) with their 95% credible intervals (CrIs), and the best probability per outcome among the 7 treatments (including placebo). WinBUGS is a Bayesian software program used to construct complex statistical models using Markov Chain Monte Carlo simulation. The first 60,000 iterations were discarded and 300,000 further iterations were run in which every 30th simulation was retained. Both fixed and random effects models were used during the analysis. WinBUGS codes used to perform mixed treatment comparison were derived from Ades et al. [20].

Sensitivity analysis was also conducted including two chains of initial values for Markov chain Monte Carlo simulation for specific previous distributions of variance parameters. The original prior distribution, gamma distribution, were replaced by a Uniform ($\sigma \sim (0,5)$) [22]. Two different sets of initials were used. Convergences were assessed by examining the autocorrelation and the Kernel density plots [23]. The model goodness of fit was assessed using residual deviance, total residual deviance and deviance information criteria (DIC) comparing between the random effects model and the fixed effects model [23].

Results

Of 1245 articles (PubMed/MEDLINE: 1180, Cochrane: 65), 304 studies were identified for further review. Reasons for excluding articles included lack of information on the medication formulation (n = 44), non-RCT (n = 67), product not marketed in Thailand (n = 82), outcomes of interest were not reported

(n= 31), access to full publication could not be obtained (n = 8), publication duplication (n = 3), study duration was less than 24 weeks (n = 7), and other reasons (n = 58). After excluding studies that did not meet our inclusion criteria, 17 were selected, representing a total of 1904 patient participants. Study selection flow is shown in **Figure 1.**

The number of patients participants per study ranged from 19–747 (median: 54). Mean of study duration was 52.3 weeks (range 24–96 weeks). Median scores of study quality assessment were 4 (range 2–5). Summary of key study parameters is shown in **Table 1.**

Six studies with placebo, 11 studies with fluphenazine, 4 studies with flupentixol, 8 studies with haloperidol, 2 studies with zuclopenthixol, 2 studies with paliperidone, and 1 study with risperidone were included in the analysis. A diagram of the network of study selection for our meta-analysis is shown in **Figure 2**.

Diagnostic criteria for schizophrenia were varied among studies and included Diagnostic and Statistical Manual III–IV, International Classification of Disease 9, Research Diagnostic Criteria, Splitzer's Criteria, Bleuler's Criteria, Schneiderian Criteria, and unspecified criteria.

There were various rating-scale based definitions of relapse used included Clinical Global Impression, Positive and Negative Syndrome Scale, Brief psychiatric Rating Scale, Comprehensive Psychological Rating Scale, Schizophrenia Change Scale, and Krawiecka–Goldberg Scale. In addition to these, a nonrating scale based definition for relapse were also used included own clinical judgment, need of additional antipsychotics, and need of hospital admission and emergency visit.

At study entry, most studies required patients to have stable symptoms for periods of time, but need of medication for relapse prevention. Some studies indicated a specific range of symptom rating scale. A comparison summary of the three outcomes for all 6 LAIs is presented in **Table 2**.

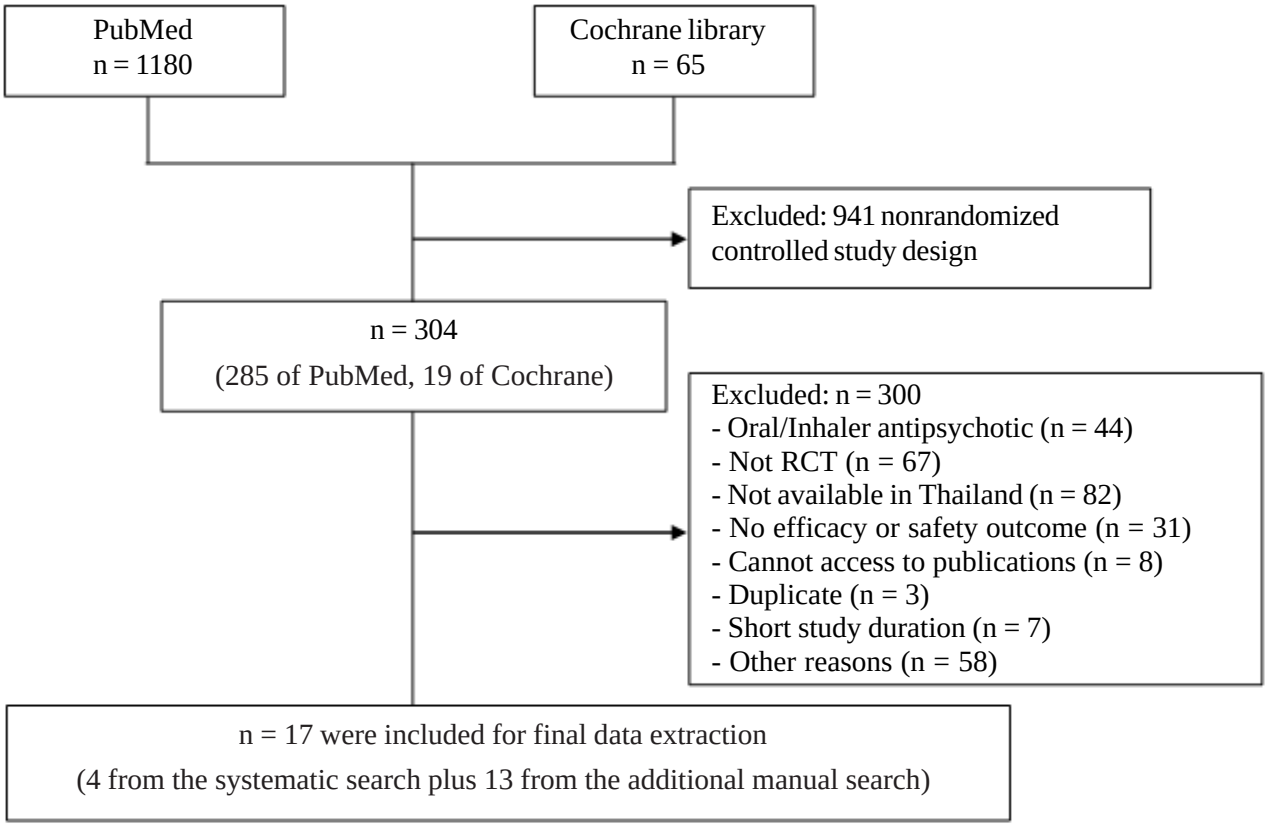

Figure 1. Study selection flow

Table 1. Summary of data reported in the randomized controlled trials included in our systematic review on long-acting injectable antipsychotics for schizophrenia

Author	Study ID	Weeks	Total patients	Jadad score	Medication and dose	Total number of patients per arm	Number of patients who have discontinuation			
							Relapse	Adverse event	Other reason	No discontinuation
Hirsch et al. 1973 [24]	1	**60**	81	2	Placebo	40	25	0	3	12
					Fluphenazine ≥ 25 mg q 4 wks	41	3	0	4	34
Odejide et al. 1982 [25]	2	**48**	53	4	Placebo	27	15	0	8	4
					Fluphenazine 50 mg q 4–8 wks	26	5	0	9	12
Sampath et al. 1992 [26]	3	**48**	16	3	Placebo	12	9	0	0	3
					Fluphenazine 17–95 mg q 2 wks	4	4	0	0	0
Eberhard et al. 1986 [27]	4	**48**	32	3	Flupentixol 10–120 mg q 4 wks	16	3	0	3	10
					Haloperidol 25–300 mg q 4 wks	16	3	0	3	10
Chouinard et al. 1985, 1989 [28, 29]	5	**32**	72	5	Fluphenazine 2.5-300 mg q 2–4 wks	36	0	0	0	36
					Haloperidol 15–900 mg q 2–4 wks	36	1	0	1	34
Cookson et al. 1986 [30]	6	**48**	19	5	Fluphenazine 12.5–37.5 mg q 2–5 wks	10	0	2	0	8
					Haloperidol 50–100 mg q 2–6 wks	9	2	0	0	7
Jolley et al. 1989, 1990 [31, 32]	7	**96**	54	4	Placebo	27	3	0	9	15
					Fluphenazine 25 mg q 4 wks	27	12	0	15	0
Kissling et al. 1985 [33]	8	**24**	54	4	Haloperidol 80 mg q 4 wks	32	1	0	9	22
					Fluphenazine 20 mg q 2 wks	22	1	5	7	9
McKane et al. 1987 [34]	9	**60**	38	4	Haloperidol 120 mg q 4 wks	19	10	0	8	1
					Fluphenazine 105 mg q 4 wks	19	10	1	6	2
Sharma and Jaigirdar 1991 [35]	10	**48**	59	4	Haloperidol ≥ 25 mg q 4 wks	30	10	4	6	10
					Fluphenazine ≥ 25 mg q 4 wks	29	6	3	3	17
Fleischhacker et al. 2012 [36]	11	**53**	747	4	Risperidone 25–50 mg q 2 wks	368	76	23	0	269
					Paliperidone 25–100 mg q 4 wks	379	99	25	0	255
Hough et al. 2010 [37]	12	**24**	408	5	Placebo	203	97	2	26	78
					Paliperidone 25–100 mg q 4 wks	205	36	3	27	139
Pinto et al. 1979 [38]	13	**72**	64	4	Flupentixol 36.6 mg three times wk	31	0	0	0	31
					Fluphenazine 25 mg three times wk	33	0	1	7	25
Wisted et al. 1983 [39]	14	**96**	32	4	Flupentixol 27 mg q 3wks	17	0	0	8	9
					Fluphenazine 31 mg q 3 wks	15	0	0	6	9
Wisted et al. 1991 [40]	15	**36**	64	3	Zuclopenthixol 100–600 mg q 4 wks	36	4	1	2	29
					Haloperidol 39–200 mg q 4 wks	28	7	1	0	20
Eklund et al. 1991 [41]	16	**48**	43	3	Placebo	23	16	0	0	7
					Haloperidol 60 mg q 4 wks	20	2	2	1	15
Dencker et al. 1980 [42]	17	**48**	60	2	Zuclopenthixol 50–600 mg q 4 wks	30	3	0	0	27
					Flupentixol 25–300 mg q 4 wks	30	4	0	3	23

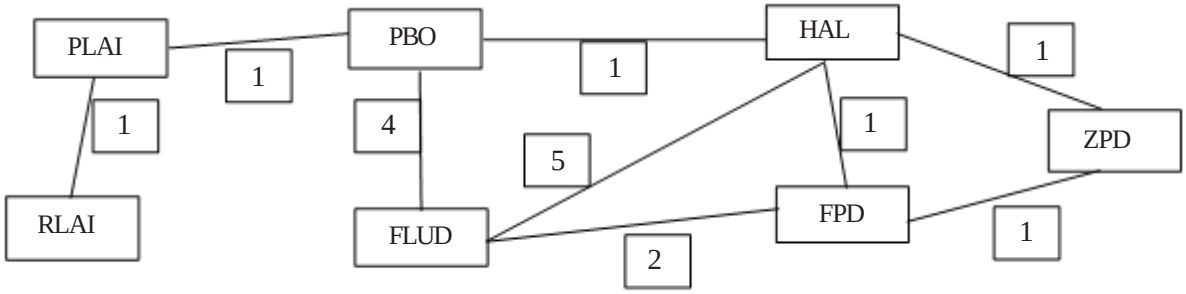

Figure 2. Network diagram. The connecting lines indicate which pairs of treatment were directly compared in randomized trials; number on lines indicate the number of trials. FLUD = fluphenazine decanoate, FPD = flupentixol decanoate, HAL = haloperidol decanoate, PBO = placebo, PLAI = paliperidone palmitate, RLAI = risperidone LAI, ZPD = zuclopenthixol decanoate

In the random effects model, placebo had the highest 52-week probability of relapse as expected. Risperidone had the lowest average 52-week probability of relapse and followed by paliperidone, zuclopenthixol, fluphenazine, flupentixol, and haloperidol, respectively. All medications had lower risk of relapse when compared with placebo, but the reduction was not significant. Without considering the placebo, zuclopenthixol had the lowest 52-week probability of discontinuation because of an intolerable adverse event or discontinuation for other reasons. However, risperidone was the best or had the highest probability of preventing relapse or discontinuation for other reasons. Zuclopenthixol was the best or had the highest probability of preventing discontinuation because of intolerable adverse events.

In the fixed effects model, most of the medications had a lower average 52-week probability of relapse than placebo, except flupentixol. By contrast with the random effects model, where no medicine presented a significant lower hazard of relapse than placebo, fluphenazine, and risperidone presented a significantly lower hazard ratio of relapse than placebo. Paliperidone presented not only the lowest 52-week probability of relapse outcome, but also the lowest 52-week probability of discontinuation because of other reasons. However, zuclopenthixol had the lowest 52-week probability of discontinuation because of an intolerable adverse event. Paliperidone was the best or had the highest probability in preventing relapse or discontinuation for other reasons. Zuclopenthixol was the best or had the highest probability of preventing discontinuation because of intolerable adverse events.

A goodness of fit model tested with total residual deviations for random effects model and fixed effects model were 104.70 and 560.70, respectively, while deviance information criteria were 5,269.63 and 36,061.40, respectively. The random effects model is more robust compared with the fixed effects model when heterogeneity is present, because the model takes into account both between-study and within-study variance. These results support for the choice of the random effects model in prediction.

Discussion

A mixed treatment comparison approach with a competing risk model was applied in our analysis. This approach supports comparison of multiple treatments, multiple outcomes, and different follow up study durations in a single analysis framework. The analysis was conducted under a Bayesian simulation framework to generate the probability of each outcome for 52 weeks for a probabilistic decision model and also provide probability for preventing the target outcomes.

Prior systemic review and meta-analysis studies of antipsychotic drugs in schizophrenia mostly compared either pairwise treatments or multiple treatments per individual target outcome [43-46]. By contrast, our study used a meta-analysis model that incorporated multiple treatments, multiple outcomes, and different follow up-times. This approach has been applied by NICE to assess antipsychotics in maintenance for schizophrenia, but we tested with LAIs instead of the oral dosage form [1, 20]. Leucht's meta-analysis showed LAIs reduced relapse more than oral antipsychotics did, but they evaluated individual target outcome separately [43].

Because we choose three competing risk outcomes in our analysis, we accept that double counting on patient number between number of relapse

Table 2. Three outcomes of 6 long acting injectable antipsychotics comparison—random effects model and fixed effects model

	Random effects model			Fixed effects model		
	Probability 52 weeks (SD)	**Hazard ratio vs placebo (95%Credible interval)**	**Probability that the medicine is best in preventing the event**	**Probability 52 weeks (SD)**	**Hazard ratio vs placebo (95%Credible interval)**	**Probability that the medicine is best in preventing the event**
Relapse						
Placebo	0.49 (0.263)	1.00	0.002 (0.046)	0.49 (0.263)	1.00	0.00 (0.000)
Fluphenazine	0.36 (0.312)	0.56 (0.13, 2.08)	0.10 (0.296)	0.21 (0.200)	0.41 (0.26 0.62)	0.06 (0.240)
Flupentixol	0.37 (0.329)	0.55 (0.05, 4.92)	0.12 (0.319)	0.49 (0.334)	22.07 (0.12, 166.10)	0.049 (0.217)
Haloperidol	0.41 (0.330)	0.71 (0.11, 3.60)	0.07 (0.259)	0.21 (0.207)	1.02 (0.23, 1.02)	0.23 (0.419)
Zuclopenthixol	0.33 (0.328)	0.32 (0.02, 4.95)	0.18 (0.386)	0.37 (0.289)	1.02 (0.07, 1.02)	0.19 (0.395)
Paliperidone	0.30 (0.314)	0.29 (0.02, 4.59)	0.18 (0.387)	0.21 (0.198)	1.01 (0.20, 1.01)	0.26 (0.437)
Risperidone	0.26 (0.321)	0.22 (0.004, 11.16)	0.35 (0.476)	0.33 (0.269)	0.97 (0.14, 0.97)	0.21 (0.409)
Discontinuation because of an adverse event						
Placebo	0.07 (0.113)	1.00	0.048 (0.213)	0.07 (0.114)	1.00	0.53 (0.499)
Fluphenazine	0.11 (0.180)	1.54 (0.39, 6.42)	0.057 (0.232)	0.21 (0.256)	6.19 (0.54, 27.41)	0.001 (0.037)
Flupentixol	0.09 (0.164)	1.12 (0.11, 7.06)	0.14 (0.343)	0.12 (0.187)	21.85 (0.15, 410.40)	0.12 (0.325)
Haloperidol	0.07 (0.147)	0.93 (0.21, 4.19)	0.16 (0.362)	0.14 (0.204)	19.64 (0.28, 19.64)	0.045 (0.208)
Zuclopenthixol	0.07 (0.159)	0.50 (0.03, 7.05)	0.31 (0.464)	0.07 (0.134)	1.01 (0.05, 3.42)	0.20 (0.403)
Paliperidone	0.13 (0.213)	1.25 (0.11, 16.55)	0.10 (0.293)	0.42 (0.377)	142.30 (0.25,142.30)	0.02 (0.145)
Risperidone	0.12 (0.218)	1.15 (0.06, 23.32)	0.20 (0.397)	0.09 (0.161)	1.06 (0.21, 6.73)	0.08 (0.271)
Discontinuation for other reasons						
Placebo	0.25 (0.246)	1.00	0.051 (0.219)	0.25 (0.247)	1.000	0.12 (0.320)
Fluphenazine	0.32 (0.299)	1.36 (0.58, 3.49)	0.07 (0.251)	0.41 (0.300)	2.20 (0.94, 6.22)	0.002 (0.039)
Flupentixol	0.31 (0.304)	1.28 (0.31, 5.12)	0.10 (0.296)	0.23 (0.263)	5.32 (0.55, 26.61)	0.19 (0.393)
Haloperidol	0.31 (0.302)	1.29 (0.48, 4.70)	0.09 (0.289)	0.50 (0.317)	19.47 (0.80, 19.47)	0.002 (0.042)
Zuclopenthixol	0.26 (0.295)	0.68 (0.08, 5.93)	0.24 (0.425)	0.21 (0.249)	0.38 (0.15, 2.62)	0.18 (0.386)
Paliperidone	0.27 (0.286)	0.80 (0.17, 3.85)	0.15 (0.357)	0.19 (0.235)	0.99 (0.51, 1.27)	0.33 (0.471)
Risperidone	0.31 (0.346)	0.81 (0.01, 54.22)	0.31 (0.461)	0.30 (0.300)	1.05 (0.04, 16.33)	0.18 (0.382)

Goodness-of-fit	**Mean (SD)**	**Mean (SD)**
Resdev1	4.9 (42.68)	168.1 (120.50)
Resdev2	43.6 (24.40)	–61.3 (92.70)
Resdev3	56.1 (36.27)	453.9 (423.70)
Total Resdev	104.7 (45.05)	560.7 (449.90)
Deviance info criteria	5,269.63	36,061.40

and number of patients with discontinuation because of treatment inefficacy might not have been avoided in some studies.

The results of the present study suggested that none of the long-acting agents are significantly better for relapse prevention than placebo, but considerable heterogeneity was found. We included stronger criteria for proven maintenance treatment effectiveness in schizophrenia by selecting only studies with duration of 24 weeks or longer. A smaller size effect for antipsychotic drugs in the longer trials than in shorter trials has been described [43]. Second, it was challenging for any treatments to show a better outcome for all three endpoints when all three were integrated into a single analysis approach.

There remains a lack of consensus between clinicians and policy makers to choose the most effective treatment available in the market. RCTs are considered the most reliable evidence for efficacy comparison; although, it is not very common for RCTs to provide a pair-wise comparison of all alternatives of interest. Therefore, synthetic evidence from available RCTs is necessary. Although RCTs were included in the current study, it is important to acknowledge that between-trial variation does exist. However, the use of a random effects Bayesian model has taken into account this variation. Therefore, the results obtained from the random effects model are more conservative and robust, providing an advantage for this approach over traditional meta-analysis. In the present study, the random effects model provided smaller total residual deviances and deviance information criteria, which means the random effects model is more favorable than the fixed effects model [20, 22].

This study has presented the use of the extension of indirect comparison or mixed treatment comparison under Bayesian analysis to obtain 52-week probabilities and relative measurements of association (hazard rate ratios), which can support health economists to use the outcomes in their evaluations. Another advantage of the present analysis is the use of a generalized linear model with a logit link function that allowed us to implement multinomial distribution for modeling hazards ratio of competing risk outcomes accompanied with Bayesian analysis using Markov chain Monte Carlo simulation. More importantly, the approach allowed different times at risk to be taken into account when estimating the log hazard ratios, instead of odd ratios when calculating pair-wise comparisons. Like typical survival analysis, it should be noted that this current analysis relies heavily on the proportional competing risk assumption and constant hazard ratios in each arm [20, 22, 46].

Nevertheless, limitations in our analysis are noted. We only considered LAIs that are available in Thailand. Therefore applying our findings in other settings with different comparative medications might show different outcomes. Our searching strategy was limited to English publications and two databases (PubMed/MEDLINE and the Cochrane library). We therefore expect our results might be different from the other systematic reviews and meta-analyses if they are able to access broader study databases or publications in languages other than English. Although some confounders were controlled through restrictive criteria, other factors such as the medication dose regimen and greater restriction of the clinical definition of end points are potential areas for future research.

Conclusion

Applying competing risk mixed treatment comparison meta-analysis under a Bayesian framework helped to integrate multiple treatments, multiple outcomes, and different follow-up times into a single analysis set. Differences on LAIs effect in reducing any treatment discontinuation or relapse outcomes were seen, but were limited in this analysis.

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Conflicts of interest statement

Osot Nerapusee and Chavalit Romyen are the employees of Janssen-Cilag Thailand, a division of Johnson & Johnson. No other authors have any conflict of interest.

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