



ORIGINAL
RESEARCH

Effectiveness of Long-Acting Injectable Antipsychotics in Schizophrenia: A Literature Review and Bayesian Meta-Analysis Informing Economic Considerations

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ABSTRACT

BACKGROUND: Although the use of long-acting injectable antipsychotics (LAIs) is considered an important option in the management of schizophrenia two recent meta-analysis, which aimed to compare LAIs vs oral antipsychotics (OAPs) in terms of relapse rate, showed discordant results.

AIM: To investigate factors affecting the efficacy of antipsychotics in terms of relapse prevention in the real-world and to estimate the management cost of an episode of relapse.

METHODS: We conducted a literature search using MEDLINE/PubMed with the aim to extract efficacy, effectiveness and adherence data of LAIs and OAPs. The primary outcome was the relative risk (RR) of relapse between two strategies. The extracted RR were included in a series of Bayesian statistical models based on the starting hypotheses. The RR rates obtained from the meta-analysis have been used as input for an economic evaluation of the total costs associated with the management of the patient with schizophrenia from the Italian NHS perspective.

RESULTS: The literature search identified 34 studies which met the inclusion criteria and were analyzed. According to the model that best explains the data, in the real-world setting the effectiveness with LAIs is greater than with OAPs, with a more pronounced effect for SGAs than for FGAs. Taking into account generation, route and frequency of administration, the RR decreased with lower administration frequency, with SGA LAI administered once every 90 days which is associated with the greatest reduction in the risk of relapse (-85%). When the results of the meta-analysis are used to feed an economic evaluation the results show that the SGA administered every 90 days is the strategy with the least expected cumulative cost both at 1 (€ 3,509) and 5 years (€ 19,690).

CONCLUSION: SGA LAIs administered every 90 days seems to be the best option for the treatment of patient with schizophrenia from both the clinical and economic perspectives.

Keywords

Long-acting injectable antipsychotics; Schizophrenia; Relapse; Italy

INTRODUCTION

Despite there have been significant pharmacological progresses and improvements in individual and community assistance, schizophrenia remains a disabling, chronic disease with alternating periods of remission and relapse. Since each subsequent relapse exacerbates the clinical deterioration of the patient, with consequent worsening of symptoms, progressive cognitive impairment, functioning deterioration, and reduced quality of life, one of the major goals of schizophrenia treatment is to prevent or delay relapse [1-5].

Long-acting injectable antipsychotics (LAIs) were introduced in clinical practice in the 1960s with the aim of overcoming the limits associated with oral antipsychotics (OAPs) in terms of treatment adherence and pharmacokinetics profile [2-7].

Although the use of LAIs is considered an important option, in particular for patients with adherence problems [2,3,5,8], two recent meta-analyzes [9,10], which aimed to compare LAIs

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vs OAPs in terms of relapse rate, showed discordant results between randomized clinical trials (RCTs) and mirror-image studies.

The first meta-analysis [10] included only RCTs lasting more than 6 months, which compared LAIs and OAPs. The primary outcome was the relapse rate at the longest study time point; secondary outcomes included the relapse rate at specific time points (3, 6, 12, 18, and 24 months), all-cause discontinuation, discontinuation due to adverse events, drug inefficacy, hospitalization and non-adherence. A total of 21 RCTs were included in the analysis and the results showed that, when pooled together, LAIs did not reduce relapse compared with OAPs. In particular, pooled LAIs only showed trend-level superiority over OAPs in preventing hospitalization (RR = 0.88; 95% CI: 0.78-1.02; $p = 0.09$) with a gradient related to the frequency of administration (longer intervals of administration were associated with a greater reduction of relapse rate) and pharmacological class (relapse rate with SGA was lower than with FGA).

Since the patients enrolled in RCTs are generally different from those in real-world studies in terms of adherence rate and illness severity, the second meta-analysis conducted by Kishimoto et al. [9] was based on 25 mirror-image studies, which better reflect the real-world setting. The study included mirror-image studies that compared period ≥ 6 months with OAPs and ≥ 6 months with LAIs in adults with schizophrenia and that reported information about hospitalization or relapse-related data. The primary outcomes were hospitalization risk and the total number of hospitalizations, while secondary outcomes included total hospitalization days and length of stay. The results of this meta-analysis show a statistically significant superiority of LAIs over OAPs in preventing hospitalization (RR = 0.43, 95% CI: 0.35-0.53; $p < 0.001$) and decreasing the number of hospitalizations (RR = 0.38; 95% CI: 0.28-0.51; $p < 0.001$).

In the light of these results we conducted a comprehensive literature review and meta-analyzed the retrieved data by use of a Bayesian hierarchical model, with the aim to investigate factors affecting the efficacy of antipsychotics in terms of relapse prevention in the real-world (effectiveness). The results of the meta-analysis have been used as input for an economic evaluation of the total costs associated with the management of the patient with schizophrenia from the Italian National Health System (NHS) perspective. Mean cumulative total cost per patient at 1 and 5 years, was calculated by antipsychotic treatment (first or second generation and administration frequency) and cost items (antipsychotic treatment and relapse management).

Methods and input data have been reviewed and approved by an Italian expert board (see Acknowledgements).

METHODS

Starting from the assumption that the antipsychotics effectiveness is a function of both their pharmacological and pharmacodynamics characteristics, on one side, and their use in real-world setting, on the other, a meta-analysis has been performed to test the following hypotheses:

1. In a real-world setting LAIs are associated with better adherence compared to OAPs;
2. In an experimental setting (RCT) a LAI and the same OAP have similar efficacy and adherence while in the real-world a net increase in the efficacy of LAI can be noted;
3. This phenomenon has a gradient and it becomes more evident when the administration is less frequent.

Literature Search and Inclusion Criteria

We conducted a literature search using MEDLINE/PubMed (last access May 18, 2017) with the aim to extract efficacy, effectiveness and adherence data of LAIs and OAPs.

The search strings (one for the search of efficacy/effectiveness data and one for the search of adherence data) have been designed on the basis of the PICOS schema (Table I), as recommended by the PRISMA guidelines [11].

Two independent investigators conducted the literature search; the revision and the selection of the studies were performed on the basis of title/abstract and then of the full-text. The electronic search through MEDLINE was supplemented by manual check of reference lists of included studies. Any disagreements were resolved by discussion or by the intervention of a third investigator.

PICOS component	Inclusion criteria	Exclusion criteria
Participants	Adults with schizophrenia	<ul style="list-style-type: none"> • Other mental disorder • Acute phase • Drug resistance • Observational cohort studies < 50 patients
Intervention	Oral or long-acting injectable monotherapy with risperidone, paliperidone, aripiprazole, olanzapine, haloperidol, fluphenazine, zuclopentixol	Any other treatment
Comparators	All (head to head, placebo, other formulation, other or none)	-
Outcome	<ul style="list-style-type: none"> • Primary: relapse rate • Secondary: treatment adherence 	Absence of adherence or relapse outcome
Study design	<ul style="list-style-type: none"> • Efficacy: interventional studies (RCT, nRCT, Uncontrolled Clinical Trial – UCT) • Effectiveness: observational studies (cohort longitudinal retrospective or prospective studies) • Adherence: observational studies (cohort longitudinal retrospective or prospective studies) 	<ul style="list-style-type: none"> • Review/meta-analyses • Case-report/case series • Preclinical studies
Other		<ul style="list-style-type: none"> • Out of objective (scope): evaluation of the effect of discontinuation therapy, switch, on-top/augmentation strategies; methodological and pharmacokinetics studies • Post-hoc or subgroup analyzes • Unavailability of full-text

Table 1. Inclusion and exclusion criteria

Data Extraction and Data Analysis

The primary outcome was the relative risk (RR) of relapse between two strategies. Therefore, we selected all the studies that compared two strategies differing in terms of active ingredient and/or administration route and/or inter-administration interval and extracted the adjusted relative risk (RR) from the text. When the relative risk was not reported, we estimated it from reported data as the ratio between absolute rates.

For RCTs we relied on the efficiency of randomization in minimizing the risk of bias, and took no further action, while for observational studies, this was done only in case of cohorts matched on risk factors for relapse, or statistically equivalent in terms of baseline characteristics. This implies that any observational study on mismatched cohorts did not contribute to the estimation of relative treatment effects.

The extracted relative risks were included in a series of Bayesian statistical models based on the starting hypotheses. In order to identify the hypothesis that best suited the data, three model sets based on alternative assumptions on the influence of administration were tested: route only, administration frequency only, or both.

For the effect of administration frequency on risk of relapse, proportional (RR depends on the *ratio* of frequencies) and additive (RR depends on the *difference* of frequencies) specifications were evaluated.

Finally, all model versions were evaluated with and without considering the generation of the AP (FGA vs. SGA).

For the relative effectiveness and economic outcome predictions, inference was based on the best model. This was identified by means of the Bayesian Information Criterion (BIC), which allows selecting the best model basing on goodness-of-fit and parsimony, with lower values indicating better performance.

The secondary outcome was the adherence, but the qualitative analysis of adherence data revealed extremely high heterogeneity in the measurement methods, in the outcomes and in the elaborations, in addition to poor reliability of the data for oral drugs. All these factors were judged to have a too high potential for bias to obtain a reliable result. For this reason adherence data were excluded from the quantitative analysis.

Economic Evaluation

The relative relapse rates obtained from the meta-analysis have been used to feed an economic evaluation of the total costs associated with the antipsychotic treatment over a time horizon of 1 and 5 years.

	OAPs (€)	LAIs (€)			
		2-weekly	3-weekly	Monthly	3-Monthly
FGA	7.9	-	14.8	10.5	-
SGA	30.2	269.6	-	287.3	287.3

Table II. Weighted average ex-factory prices

FGA OAP = haloperidol; SGA OAP = paliperidone, risperidone, olanzapine, aripiprazole; SGA 2-weekly = olanzapine, risperidone; FGA 3-weekly = fluphenazine; FGA monthly = haloperidol; SGA monthly = paliperidone, olanzapine, aripiprazole; SGA 3-monthly = assumed equal to SGA monthly

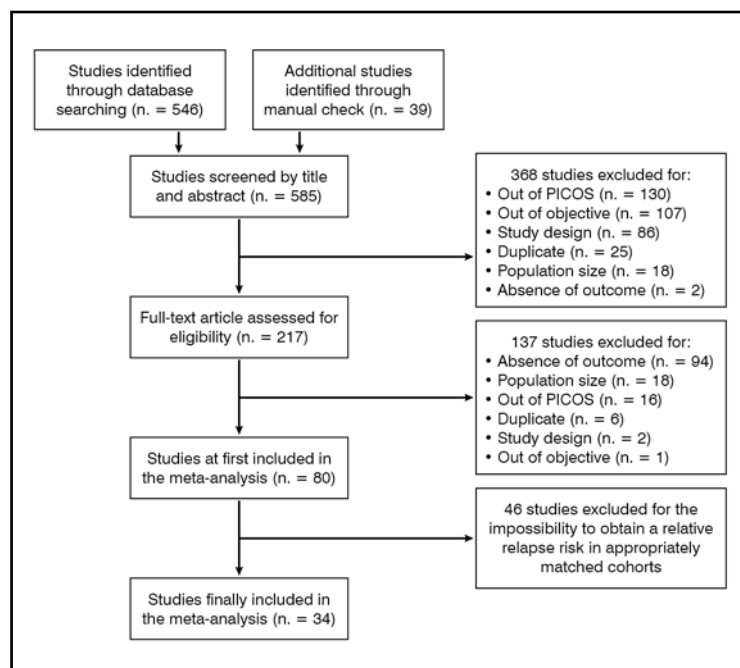


Figure 1. Flowchart of literature search

culated taking into account both hospitalization and the subsequent stay in residential facilities. In order to better represent the Italian context, the mean cost between Lazio, Lombardy, and Tuscany was used in the economic evaluation. The cost considered by the experts comprises the hospitalization for the acute phase for 10-15 days (proxied with the regional tariffs) and the following rehabilitation in a dedicated institution for a mean of 30 days: the resulting mean cost per relapse is € 10,500.

In the 5-year scenario every relapse increases the subsequent relapse rate by 20% [15,16].

RESULTS

Search and Study Characteristics

The literature search identified 546 studies, plus 39 studies added through manual check, for a total of 585 studies. Of these, 368 studies were excluded after the screening by title and abstract and 217 were fully inspected. Finally, 34 studies (20 RCTs) met the inclusion criteria and were analyzed (Figure 1). The details of the studies included are presented in Table III [17-50].

Reference	Comparators	Patients (n.)	Relative efficacy/ effectiveness	Data extracted
Observational studies [17-30]				
Baser, 2015	PAL 30 vs. SGA OAPs	335 vs. 335	0.623	Ratio between absolute rates in propensity score matching
Bitter, 2013	RIS 14 vs. ARI oral	1095 vs. 601	0.640	Ratio between absolute rates in propensity score matching

Table continues >

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Reference	Comparators	Patients (n.)	Relative efficacy/ effectiveness	Data extracted
Bitter, 2013	RIS 14 vs. OLA oral	1095 vs. 1633	0.767	Ratio between absolute rates in propensity score matching
Bitter, 2013	RIS 14 vs. RIS oral	1095 vs. 2480	0.387	Ratio between absolute rates in propensity score matching
Grimaldi-Bensouda, 2012	RIS 14 vs. OAPs	400 vs. 784	0.490	Adjusted RR from text
Guo, 2011	OLA oral vs. ARI oral	149 vs. 132	0.947	Ratio between absolute rates
Joshi, 2016	PAL 30 vs. RIS 14	499 vs. 499	0.720	Adjusted OR from text
Lafeuille, 2015	PAL 30 vs. OAPs	374 vs. 32475	0.750	HR from text
Marcus, 2015	FLU 14-42 vs. OAPs	45 vs. 3428	0.870	Adjusted OR from text
Marcus, 2015	ALO 28 vs. OAPs	112 vs. 3428	0.910	Adjusted OR from text
Marcus, 2015	RIS 14 vs. OAPs	81 vs. 3428	0.670	Adjusted OR from text
Marcus, 2015	PAL 30 vs. OAPs	102 vs. 3428	0.530	Adjusted OR from text
Morrato, 2015	PAL 30 vs. SGA OAPs	201 vs. 595	0.860	Adjusted OR from text
Ren, 2011	RIS 14 vs. OAPs	924	0.743	Ratio between absolute rates
Schreiner, 2014	RIS 14 vs. SGA OAPs	426 vs. 490	0.654	Ratio between absolute rates
Tiihonen, 2006	OLA oral vs. ALO oral	822 vs. 107	0.540	Adjusted RR from text
Tiihonen, 2006	RIS oral vs. ALO oral	651 vs. 107	0.890	Adjusted RR from text
Tiihonen, 2011	RIS 14 vs. RIS oral	51 vs. 411	0.570	Adjusted HR from text
Tiihonen, 2011	ZUC 14 vs. ZUC oral	30 vs. 6	0.490	Adjusted HR from text
Tiihonen, 2011	ALO 28 vs. ALO oral	6 vs. 9	0.120	Adjusted HR from text
Tiihonen, 2017	RIS 14 vs. RIS oral	3021 vs. 7016	0.859	Ratio between adjusted HR vs. no treatment from text
Tiihonen, 2017	ZUC 14 vs. ZUC oral	4083 vs. 3425	0.791	Ratio between adjusted HR vs. no treatment from text
Tiihonen, 2017	OLA 14 vs. OLA oral	400 vs. 1173	0.921	Ratio between adjusted HR vs. no treatment from text
Tiihonen, 2017	ALO 28 vs. ALO oral	1632 vs. 3348	0.790	Ratio between adjusted HR vs. no treatment from text
Voss, 2015	PAL 30 vs. OAPs	109 vs. 109	0.540	HR from text
RCT [31-50]				
Alphs, 2015	PAL 30 vs. OAPs	226 vs. 218	0.681	Ratio between absolute rates
Buckley, 2014	RIS 14 vs. OAPs	146 vs. 150	1.285	Ratio between absolute rates
Carpenter, 1999	FLU 14 vs. FLU 42	25 vs. 25	0.763	Ratio between absolute rates
Csernansky, 2002	ALO oral vs. RIS oral	188 vs. 177	1.930	RR from text
Detke, 2014	OLA 28 vs. OLA oral	264 vs. 260	1.086	Ratio between absolute rates
Fleischhacker, 2014	ARI 28 vs. ARI oral	265 vs. 266	0.985	Ratio between absolute rates
Glick, 2002	OLA oral vs. ALO oral	541 vs. 158	0.828	Ratio between absolute rates
Hogarty, 1979	FLU 14 vs. FLU oral	27 vs. 25	0.862	Ratio between absolute rates
Ishigooka, 2015	ARI 28 vs. ARI oral	228 vs. 227	0.920	Ratio between absolute rates
Kane, 2009	OLA oral vs. ARI oral	281 vs. 285	0.985	Ratio between absolute rates
Kane, 2010	OLA 14 vs. OLA oral	281 vs. 322	1.500	Adjusted HR from text
Kane, 2010	OLA 28 vs. OLA oral	318 vs. 322	1.400	Adjusted HR from text
Kane, 2010	OLA 14 vs. OLA 28	281 vs. 318	1.000	Adjusted HR from text
Keks, 2007	RIS 14 vs. OLA oral	247 vs. 300	1.170	Ratio between absolute rates
Kim, 2008	RIS 14 vs. RIS oral	22 vs. 28	0.307	Ratio between absolute rates
Lieberman, 2005	OLA oral vs. RIS oral	330 vs. 333	0.575	Ratio between absolute rates
Malla, 2016	RIS 14 vs. OAPs	42 vs. 35	1.894	Ratio between absolute rates
McEvoy, 2014	PAL 30 vs. ALO 28	145 vs. 145	1.294	Ratio between absolute rates
Rosenheck, 2011	RIS 14 vs. OAPs	187 vs. 182	0.870	Adjusted HR from text
Savitz, 2016	PAL 90 vs. PAL 30	483 vs. 512	0.870	HR from text
Schooler, 1980	FLU 21 vs. FLU oral	107 vs. 107	0.668	Ratio between absolute rates
Schooler, 2005	RIS oral vs. ALO oral	197 vs. 203	0.864	Ratio between absolute rates

Table III. Details of the studies included in the meta-analysis

ALO = haloperidol; ARI = aripiprazole; FLU = fluphenazine; OAP = oral antipsychotics; OLA = olanzapine; PAL = paliperidone; RIS = risperidone; SGA = second generation antipsychotics; ZUC = zuclopentixol

Treatment effect	FGA: LAIs vs. OAPs	SGA: LAI vs. OAPs	SGA vs. FGA	+7 days ¹
RR [95% CI]	0.80 [0.69-0.93]	0.53 [0.48-0.58]	0.79 [0.58-1.09]	0.90 [0.80-1.00]
Credibility ² (%)	99.8	100	93.4	97.2

Table IV. Best model results (real-world)

¹ Each additional 7 days of inter-dose interval

² Posterior probability of superiority, measured as percentage of iterations with RR < 1

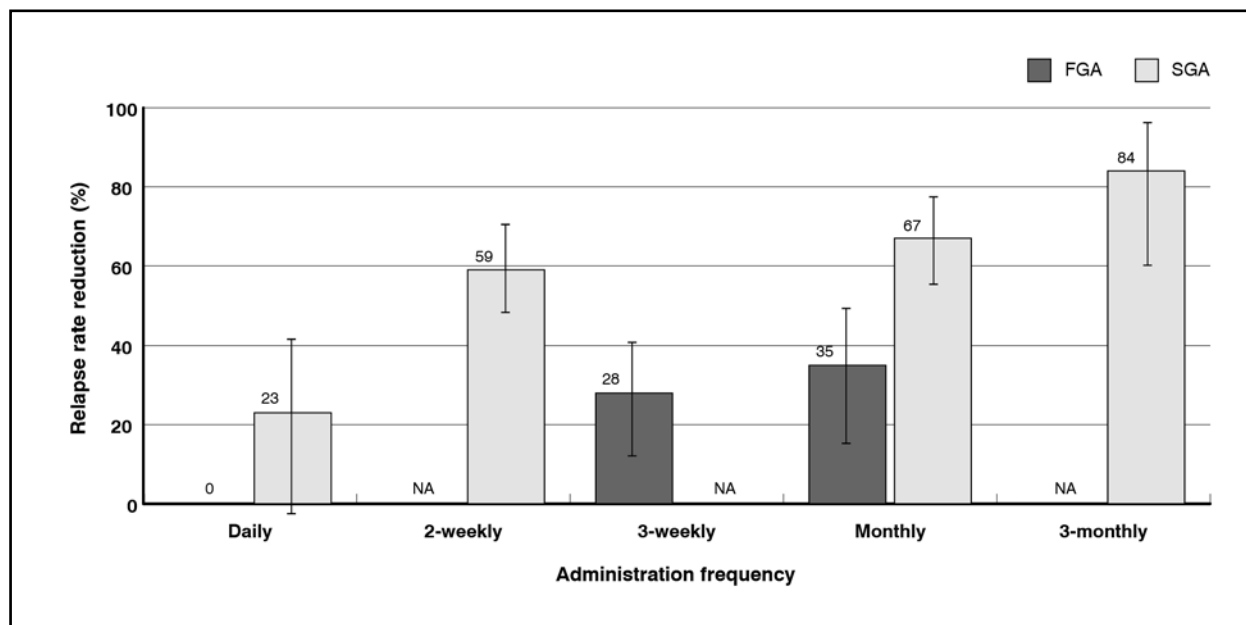


Figure 2. Relapse rate reduction vs oral FGA according to class and administration frequency

- Common results of all tested models indicate that:
- In real-world setting, the effectiveness is greater with LAIs than with orals– this effect is more pronounced for SGAs than for FGAs, while the route has no statistically significant effect under experimental conditions;
- In real-world settings the effectiveness significantly increases with decreasing administration frequency;

There are high probabilities (80-95% in the best fitting models) that the intrinsic efficacy of SGAs is greater than that of FGAs.

The model best explaining the data was the one that comprises both the effect of route and frequency of administration (additive effect) and that considers a class effect (FGAs vs. SGAs) for both intrinsic efficacy and administration route effect (Table IV).

- According to this model:
- In the real world setting, a LAI reduces the risk of relapse, compared to the same AP given by the oral route, by 20% (RR = 0.8) if it belongs to the first generation, and by almost 50% (RR = 0.53) if a SGA;
- In the real world setting, the risk of relapse is reduced by 10% (RR = 0.9) for each additional week of inter-dose interval;

Second generation agents reduce the risk of relapse by almost 20% (RR = 0.79) when compared to FGAs of equivalent route and frequency of administration.

Figure 2 shows the relative risks (vs. FG OAP, taken as reference) for all considered combinations of generation, route, and frequency of administration inferred by the model. As can be seen, relapse rate decreased with lower administration frequency, and the greatest reduction in the risk of relapse is expected with the use of a SGA LAI administered once every 90 days, associated with an estimated RR of 16%, i.e. a reduction of 84% in the frequency of relapse, compared to the use of an oral, first generation, antipsychotic agent.

Credibility of results (i.e. posterior probability of superiority, measured as percentage of iterations with RR < 1 - data not shown) resulted close to certainty (98-100%) for the comparison of any LAI vs. any OAP, while there is substantial uncertainty in the comparison of oral SGAs versus first generation LAIs.

Administration frequency	Total cost per patient (€)			
	1 year		5 years	
	FGA	SGA	FGA	SGA
Daily	6,086 [4,112-8,472]	4,753 [3,425-6,332]	45,180 [30,480-62,950]	34,930 [25,060-46,670]
2-weekly	NA	5,085 [4,285-6,064]	NA	31,370 [25,590-38,570]
3-weekly	4,493 [2,793-6,697]	NA	33130 [20460-49520]	NA
Monthly	4,022 [2,380-6,196]	4,786 [4,085-5,643]	29710 [17480-45870]	28,720 [23,670-34,930]
3-monthly	NA	3,795 [3,045-5,275]	NA	21,270 [15,940-32,350]

Table V. Mean [95% CrI] cumulative total cost per patient at 1 and 5 years, by antipsychotic treatment

Administration frequency	Probability SGA 90-day less costly (mean delta) vs.			
	FGA	SGA	FGA	SGA
	After 1 year		After 5 years	
Daily	98% (2,291 €)	87% (958 €)	100% (23,910 €)	97% (13,660 €)
2-weekly		96% (1,290 €)		96% (10,100 €)
3-weekly	77% (698 €)		97% (11,860 €)	
Monthly	58% (227 €)	97% (991 €)	93% (8,440 €)	97% (7,450 €)

Table VI. Probability that the cumulative total cost per patient of alternative strategies is higher than SGA 90-day at 1 and 5 years, and their mean cost increase

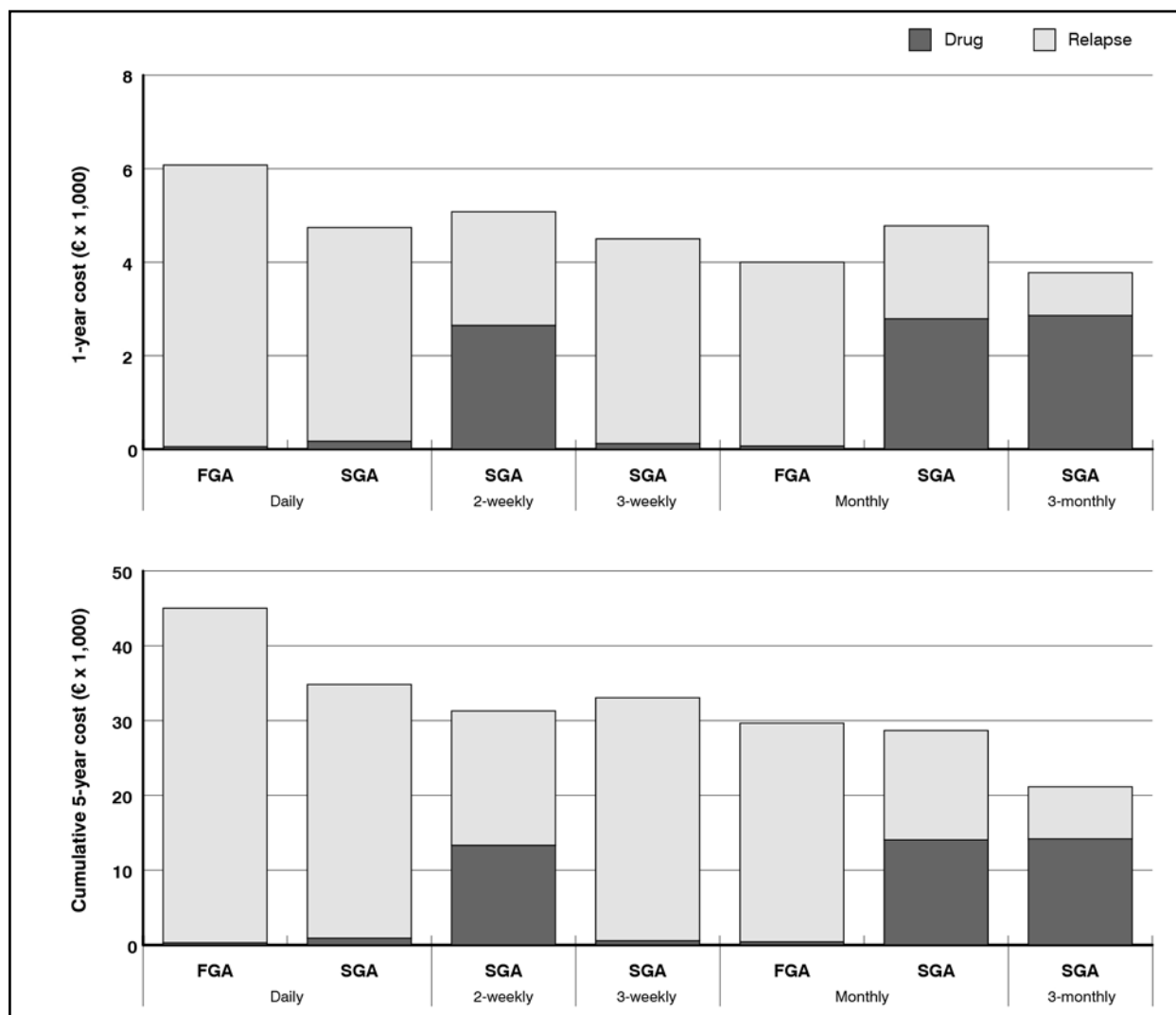


Figure 3. Mean cumulative total cost per patient at 1 and 5 years, by antipsychotic treatment and cost items

Economic Evaluation

The average (95% CrI) cumulative 1 year and 5 year cost for the management of a patient with schizophrenia estimated by the model for the available strategies are shown in Table V.

The data indicate that the strategy with the least expected cumulative cost is SGA administered every three months, already at one year, and more so in the medium term (5 years), with 91% (data not shown) chances of being the least costly strategy (Table VI).

Observing the contribution of the single cost items to the total (Figure 3), it can be seen how the component related to the drug acquisition becomes more prevalent moving from the least to the most effective treatments, and how this trend becomes more evident with longer time horizons.

DISCUSSION

Long-acting injectable antipsychotics (LAIs) were introduced in the treatment of schizophrenia with the aim of improving treatment adherence and pharmacokinetics profile associated with OAPs.

Our meta-analysis, which aimed to investigate factors affecting the efficacy of antipsychotics in terms of relapse prevention in the real-world (effectiveness), shows that in the real-world setting the effectiveness with LAIs is greater than with OAPs, with a more pronounced effect for SGAs than for FGAs. In particular, a LAI reduced the risk of relapse by 20% and 50%, as compared to the same AP given by oral route and belonging to the first and the second generation, respectively. Furthermore, in the real-world setting the effectiveness significantly increases with decreasing administration frequency, with a relative reduction in the risk of relapse equal to 10% for each additional week of inter-dose interval. Taking into account generation, route and frequency of administration our results show that, taking FGA OAP as reference, the relapse rate decreased with lower administration frequency, with SGA LAI administered once every 90 days which is associated with the greatest reduction in the risk of relapse (-84%). As shown in Table III, only one RCT that compares 90-day LAI was included in the meta-analysis [48]. This trial involved 1016 patients who were randomly assigned to 90-day paliperidone or 30-day paliperidone and showed noninferiority of the 3-month formulation in terms of relapse rate. The results demonstrated the noninferiority of the 3-monthly administration in terms of relapse rate and the mITT analysis showed that the nominal hazard ratio for a patients switching from 90-day ($n = 483$) to 30-day ($n = 512$) formulation was 0.87 (95% CI: 0.56-1.34).

When the results of the meta-analysis are used to feed an economic evaluation, in order to estimate the management cost of an episode of relapse, the results show that the SGA administered every 90 days is the strategy with the least expected cumulative cost at 1 and 5 years (€ 3,795 and € 21,270, respectively).

Observing the composition of the single cost items (relapse management and drug cost) it can be seen that the cost for relapse management decreases moving from the daily administration to less frequent administration schedules. Furthermore, even if the component related to the drug acquisition becomes more prevalent moving from the least to the most effective treatment, the clinical advantage in terms of relapse prevention compensates the drug cost, resulting in a lower total expenditure.

Our conclusions are in line with a recent systematic review, which aimed to investigate the economic impact of schizophrenia on the healthcare system in Europe and to identify the most important cost driver in the management of schizophrenia [51]. According to Kovacs et al. the component related to the hospital stay represents the major direct cost of schizophrenia, accounting for 27% to 92% of total direct medical costs, depending on the country considered. Among the suggestions given by the Authors in order to reduce the economic burden associated with schizophrenia and to improve the allocation of financial resources, there are the reduction of the number of hospitalizations and the improvement of persistence and adherence in antipsychotic therapy [51].

At the light of these results, it can be said that more efforts are needed in order to improve the management of patients with schizophrenia and to enhance identification of patients who can benefit most from the treatment with LAIs achieving better clinical and economic outcomes.

The main limitation of our study is the inclusion in the meta-analysis of only one trial that compares 90-day vs. 30-day administration, however, due to the structure of the model, comparing strategies with differing administration frequency, provide information about the effect of the extension of the administration interval.

CONCLUSION

Since one of the major goal of the treatment of schizophrenia is to prevent/delay relapse, at the light of our results SGA LAIs administered every 90 days seems to be the best option from both the clinical and economic perspectives.

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Conflict of interest

OZ, GG, and MP are employees of Adres, which has received project funding by Janssen-Cilag SpA for the conduct of the study.

LP is co-owner and employee of Adres, which has received project funding by Janssen-Cilag SpA for the conduct of the study. LP is an editorial member of *Farmeconomia. Health Economics and Therapeutic Pathways*.

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