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REAL-WORD EFFECTIVENESS AND COST CONSEQUENCE OF ANTIPSYCHOTIC TREATMENT CHOICES IN THE TREATMENT OF SCHIZOPHRENIA IN ITALY: A BAYESIAN HIERARCHICAL INFERENCE MODEL

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Objective

- 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.
- Two recent meta-analyses [1,2], showed a different magnitude of efficacy of LAIs vs. OAPs in reducing hospitalization, in RCT setting (risk ratio [RR]=0.88, p=0.09) or in real-world (RR=0.38, p<0.001), suggesting a significant effect of adherence in the antipsychotics (APs) efficacy.
- A Bayesian hierarchical model was developed to model and investigate factors affecting the efficacy of APs and to estimate their real-life impact in terms of overall disease management cost.

Methods

Literature search

- MEDLINE/PubMed (last access May 20, 2022), search string based on the PICOS schema in figure:

	Component	Inclusion criteria	Exclusion criteria
P	Participants	Adults with schizophrenia	Other mental disorder, acute phase, drug resistance, sample < 50 patients*
I	Intervention	OAPs or LAIs (monotherapy with risperidone, paliperidone, aripiprazole, olanzapine, haloperidol, fluphenazine, zuclopentixol)	Any other treatment
C	Comparators	All type (head-to-head, placebo, other formulation, other or none)	-
O	Outcome	Relapse risk (adjusted risk ratio of relapse for observational studies)	Absence of adherence, effect of discontinuation, switch, relapse outcome
S	Study design	Interventional studies (RCT, nRCT, UCT) for efficacy; observational studies (cohort longitudinal retrospective or prospective studies) for effectiveness and adherence	Review, meta-analyses, case report/series, preclinical studies, post-hoc/subgroup analysis

* Only for observational studies; RCT: randomized clinical trial; nRCT: non RCT; UCT; uncontrolled clinical trial

Model structure

- The statistical model was constructed in WinBUGS to estimate the RR of relapse between two strategies as a function of: (1) active substance (intrinsic efficacy), (2) administration route (parenteral vs. oral), (3) AP generation (second- vs. first-generation, SG vs. FG), and (4) inter-administration interval.
- Administration route, AP generation, and inter-administration interval were adjusted by study design (controlled vs. observational).
- Effect of administration frequency was modeled both as proportional (RR depends on the ratio of frequencies) and additive (RR depends on the difference of frequencies). Results were presented as mean and 95% credibility interval (CrI).

Economic input

- The RR of relapse obtained from the statistical model were used to feed an economic evaluation of the total costs associated with the antipsychotic treatment (time horizon 1 and 5 years) from the Italian NHS perspective (only direct costs considered).
- After the first episode, the risk of subsequent relapse increased by 20% [3,4].
- Drug costs were calculated considering the treatment mix for Italy in 2022 and assuming 50% adherence for OAPs, 71% for FG LAIs, and 82% for SG LAIs [5,6].
- Cost of each relapse was calculated considering both hospitalization in the acute phase and the rehabilitation in residential facilities (€ 10,500) [6].

Results

- 50 studies (20 RCTs + 30 observational) reporting on 71 direct comparisons met inclusion criteria (Figure 1).
- According to Bayesian Information Criteria, the model best explaining the data was the one that assumed proportional effect of administration frequency.
- In real-world setting, the effectiveness increases with decreasing administration frequency and is greater with LAIs than with orals (Table 1), this effect is more pronounced for SG LAIs (RR=0.69, 95% CrI 0.66 to 0.71) than for FG LAIs (RR=0.81, 95% CrI 0.78 to 0.84).
- Considering combinations of generation, route, and frequency of administration inferred by the model, relapse risk decreases with lower administration frequency (Table 2). The greatest efficacy in the risk of relapse (vs. FG OAPs) is expected with the use of SG LAIs administered once every 6 months (RR=0.21, 95% CrI 0.06 to 0.54), followed by SG LAIs administered once every 3 months (RR=0.36, 95% CrI 0.21 to 0.59). Details for each drug in Figure 2.
- Economic evaluation results in Table 3 show that the least expected cumulative cost is associated to SG LAIs administered every 6 months, with about 40% probability to be less costly than any other strategy at 1 year (saving € 978) and almost 90% at 5 years (savings € 12,626).
- Observing the composition 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. However, relapse costs decrease moving to more dilated interval dose frequencies.

Figure 1. Systematic review flow diagram.

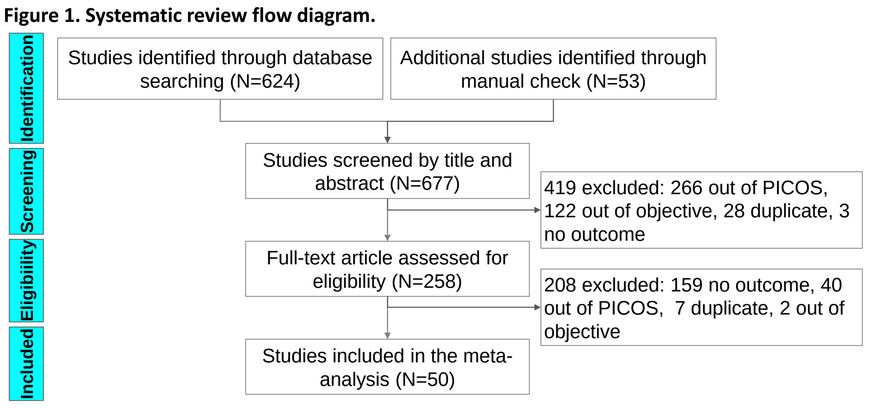

Figure 2. Relapse risk reduction (vs. oral haloperidol) in the real-world setting.

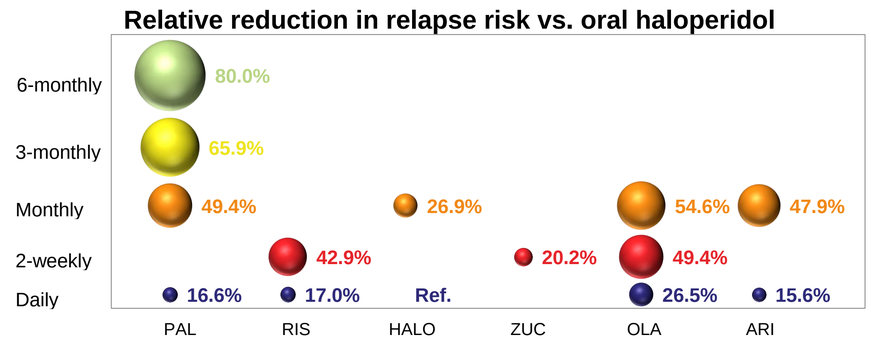

Figure 3. Mean cumulative total cost per patient by AP treatment and cost items.

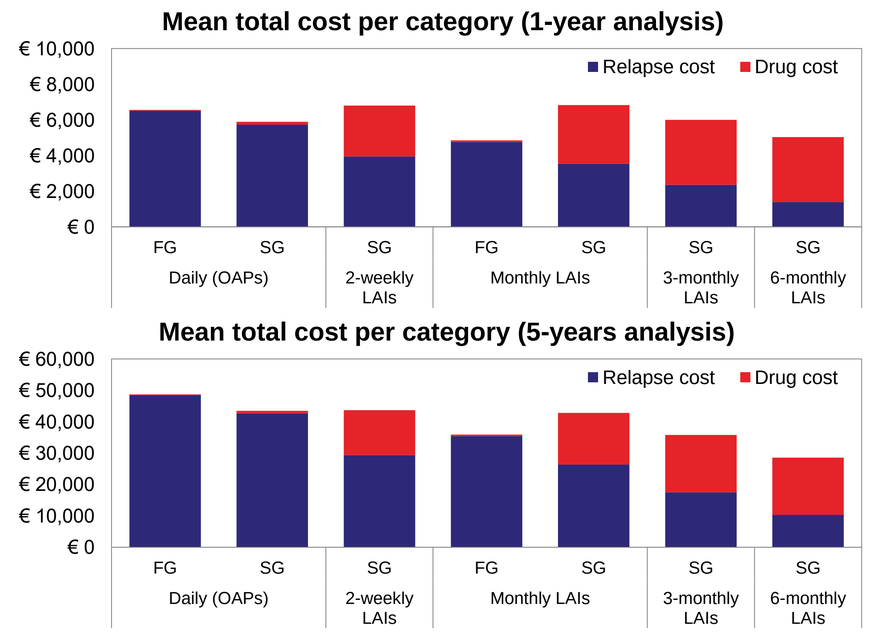

Table 1. Treatment characteristics effecting APs efficacy in the real-world setting.

Comparison	RR (95% CrI)	Credibility*
FG LAIs vs. OAPs	0.81 (0.78 to 0.84)	100%
SG LAIs vs. OAPs	0.69 (0.66 to 0.71)	100%
SG vs. FG LAIs	0.85 (0.65 to 1.08)	91.4%
Inter-dose interval double-up	0.90 (0.81 to 0.99)	98.3%

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

Table 2. Relapse RR (95% CrI) vs. oral FGA in the real-world setting.

Frequency	FG LAIs	SG LAIs
Daily (OAPs)	Ref.	0.89 (0.69 to 1.15)
2-weekly LAIs	NA	0.61 (0.47 to 0.79)
Monthly LAIs	0.73 (0.66 to 0.81)	0.55 (0.43 to 0.71)
3-monthly LAIs	NA	0.36 (0.21 to 0.59)
6-monthly LAIs	NA	0.21 (0.06 to 0.53)

Table 3. Probability that the cumulative total cost per patient of alternative strategies was higher than SGA 6-monthly LAIs at 1 and 5 years (mean cost increase in brackets).

Frequency	1 year		5 years	
	FG LAIs	SG LAIs	FG LAIs	SG LAIs
Daily (OAPs)	90.2% (€ 1,528)	80.4% (€ 854)	98.2% (€ 20,170)	95.5% (€ 14,880)
2-weekly LAIs	NA	95.3% (€ 1,767)	NA	96.6% (€ 15,090)
Monthly LAIs	42.1% (-€ 182)	97.2% (€ 1,798)	88.3% (€ 7,330)	97.6% (€ 14,250)
3-monthly LAIs	NA	98.3% (€ 968)	NA	98.3% (€ 7,200)
Any other APs	**40.7% (€ 978)**		**87.4% (€ 12,626)**	

Conclusions

Since one of the major goal of the treatment of patient with schizophrenia is to prevent/delay relapse, at the light of our results SG LAIs administered every 6 months seems to be the best option from both the clinical and economic perspectives, followed by SG LAI administered every 3 months. Reduction of relapse cost is a direct consequence of a better disease control and improvement in quality of life.

References

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AP: antipsychotics; CrI: credibility interval; FG: first-generation; LAI: Long-acting injectable antipsychotics; nRCT: non RCT; OAP: oral antipsychotics; RCT: randomized clinical trial; RR: risk ratio; SG: second-generation; UCT; uncontrolled clinical trial; SG: second-generation

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