Farmeconomia. Health economics and therapeutic pathways 2024; 25(1): 9-17
https://doi.org/10.7175/fe.v25i1.1558

ORIGINAL RESEARCH

Optimizing Treatment of Schizophrenia: Clinical and Economical Potential for Patient Switching to Long-Acting Injectables

Orietta Zaniolo [1], Silvia Maffezzoli [2], Massimiliano Povero [1], Lorenzo Pradelli [1]

[1] AdRes – Health Economics & Outcome Research, Turin

[2] Johnson&Johnson, Milan

ABSTRACT

INTRODUCTION: Long-acting injectable antipsychotics (LAIs), due to a lower frequency of administration, could address the well-established challenge of non-adherence to oral ones. We conducted a Network Meta-Analysis (NMA) to assess the relationship between administration frequency and effectiveness. The recent introduction of a semi-annual paliperidone palmitate formulation, along with the arrival of monthly paliperidone generics, could emphasize LAI's advantages. Aim of this paper is to present the results derived from an updated version of our previous NMA. These results are used to fuel a budget impact model built to evaluate the economic implications of optimizing dosing intervals.

METHODS: We compare the current distribution of patients among available LAI active substances and dosing frequencies with an optimized scenario. In this scenario, 20% of patients are switched to the next permitted regimen with a longer inter-dosing interval. Drug acquisition costs and relapse management costs are taken into account over a one-year simulation period; these last items are estimated by means of the event rates obtained from the updated meta-analysis. The optimized scenario incorporates the reduced cost resulting from the expiration of patents.

RESULTS: Throughout the analysis, a total of 11,600 patients were able to switch from shorter to longer dosing intervals, leading to an overall optimization of quality of care. The greater expenditure incurred by the Italian National Health Service (NHS) in the acquisition of newer and longer-lasting drugs is offset by savings associated with the arrival of generics of monthly paliperidone palmitate and the shift toward less-relapsing regimens. The net impact on the NHS budget is a saving of more than 19 million Euros.

CONCLUSION: This economic saving has the potential to initiate a virtuous process: it could be reinvested to fund a further shift from oral daily therapies, which are less expensive but marked by poor compliance, to LAIs. According to our simulation, nearly 40 thousand patients could undergo this transition, without additional expenses for the NHS.

Keywords

Budget impact analysis; Network Meta-Analysis; Semi-annual formulation; Paliperidone palmitate; Adherence

INTRODUCTION

Non-adherence to oral antipsychotics (OAPs) has been established as a leading cause of relapse and general difficulty in the treatment of schizophrenia. In the early stages of schizophrenia, about 50% of patients exhibit nonadherence to oral drugs [1,2] and more than 70% discontinues treatment within 18 months [3]. Non-adherence has notable clinical and public health implications, increasing personal suffering, caregiver burden, and utilization of acute-care services. Long-acting injectable (LAI) antipsychotics were developed with the goal of promoting medication adherence and, in general, better symptom management. LAIs eliminate the need for daily dosing, provide stable medication exposure, and enable regular monitoring of dose administration. Furthermore, patients who adhere to antipsychotic medications are more likely to also adhere to medications for comorbid cardiometabolic conditions, thereby improving overall outcomes [4]

These considerations are further confirmed by the results of two meta-analyses comparing LAIs vs. OAPs in terms of relapse rate in randomized clinical trials (RCTs) [5] and obser-

Corresponding author
Orietta Zaniolo
o.zaniolo@adreshe.com
Received: 28 February 2024
Accepted: 3 April 2024
Published:22 April 2024

vational studies [6]. In the analysis including only RCTs lasting more than 6 months, LAIs did not reduce relapse compared with OAPs; in particular, they only showed trend-level superiority in preventing hospitalization (RR = 0.88, p = 0.09). Since patients enrolled in RCTs are generally different from those in real-world studies in terms of adherence rate and illness severity, itis not surprising that the analysis based on 25 mirror-image studies [6], that better reflect the real-world setting, shows a statistically significant superiority of LAIs over OAPs in decreasing the number of hospitalizations (RR = 0.38; CI 95%: 0.28-0.51; p < 0.001).

A few years ago, this inconsistency led us to further investigate these dynamics using a Network Metanalysis (NMA) to estimate the magnitude of the clinical effect associated with improved adherence with LAI [7]. A Bayesian hierarchical model was designed on the basis of the hypotheses we wanted to test: in a real-world setting, LAIs are associated with better adherence compared to OAPs. In an experimental setting, a LAI and the same OAP have similar efficacy and adherence, whereas in the real-world, a net increase in the efficacy of LAI can be noted; this phenomenon has a gradient and becomes more evident when the administration is less frequent [7]. We conducted a comprehensive literature search with the aim to extract the relative risk of relapse between strategies differing in terms of active ingredient and/or administration route and/or inter-administration interval. Thirty-four studies met the inclusion criteria and were analyzed. The extracted data were included in three Bayesian statistical model sets based on alternative assumptions about the influence of administration on effectiveness (route only, administration frequency only, or both). The model best explaining the data was the one that included both the effect of route and frequency (with an additive effect) and considered a class effect (Typical vs. Atypical). The relapse rate decreased with lower administration frequency, with the greatest reduction (84%) expected with the use of atypical LAI administered once every 90 days compared with the use of an oral, first-generation, antipsychotic agent.

The secondary outcome of our previous analysis was adherence; however, the qualitative analysis of adherence data revealed extremely high heterogeneity in both the measurement and elaboration methods, leading to the exclusion of adherence data from the quantitative analysis.

Starting from previously obtained results, we proceeded into their update, also to include in the evaluation the recently introduced semi-annual formulation of paliperidone palmitate. Here we present the results from the updated NMA in terms of relapse rates for each regimen and show the pharmacoeconomic consequences of a gradual transition toward lower frequency LAIs, including the expected reduction of costs associated with relapse management.

METHODS

Scenarios

A budget impact model was developed to compare two scenarios over a 1-year simulation period: the current distribution of patients across available LAI active substances and dosing frequencies and an optimized scenario where a share of patients—from here, indicated as transition rate—was switched to the next permitted regimen with a longer inter-dosing interval.

Target patients feeding both scenarios were Italian patients [8] with a diagnosis of schizophrenia [9] treated with LAI antipsychotics (MS Janssen internal data).

The current distribution of patients among different frequencies and active substances was based on IQVIA sales data for the years 2018-2022 (Table I)

Administration interval	MS (%)	Active substances	MS intra-interval (%)
Every 2 weeks	9	Risperidone	91.0
		Olanzapine	9.0
Monthly	75	Olanzapine	1.7
		Risperidone	-
		Aripiprazole	49.6
		Paliperidone	48.7
Quarterly	16	Paliperidone	100.0
Semi-annual	-	Paliperidone	-

Table I. *Current distribution of patients with diagnosis of schizophrenia among atypical LAI antipsychotics*
MS: market share

The optimized scenario was constructed from the current base by applying of the transition rate to its market shares. This rate was set at 20% and thus acts twice during the time horizon (every six months) to respect a minimum stabilization period (four months or more), as recommended by the Summary of Product Characteristics (SPC) for patients treated with monthly frequency. The transition rate was applied in a uniform way and, obviously, only on the treatments for which SPCs recommend the switch toward a regimen with a longer inter-dosing interval. The

	Component	Inclusion criteria	Exclusion criteria
P	Participants	Adults with schizophrenia	Other mental disorder; Acute phase; Drug resistance; Observational cohort studies < 50 patients
I	Intervention	Oral or long-acting injectable monotherapy with risperidone, paliperidone, aripiprazole, olanzapine, haloperidol, fluphenazine, zuclopentixol	Any other treatment
C	Comparators	All (head-to-head, placebo, other formulation, other or none)	-
O	Outcome	Relapse rate	Impossibility to obtain HR in appropriately matched cohorts
S	Study design	Interventional studies (RCT, nRCT, UCT) for efficacy; observational studies (cohort longitudinal retrospective or prospective studies) for effectiveness	Review/meta-analyses; Case-report/case series; Preclinical studies

Tabella II. *Inclusion and exclusion criteria*
HR = hazard ratio; RCT = randomized controlled trial; nRCT = non RCT; UCT = uncontrolled clinical trial

transitions considered here were the switch from risperidone every 2 weeks to monthly paliperidone or risperidone, the switch from monthly paliperidone toward the quarterly formulation, and from quarterly to semi-annual formulation. Market shares of the other drugs were kept constant and equal in the two scenarios. The direct switch from monthly paliperidone to the semi-annual formulation was set at zero: this decision was essentially due to uncertainty regarding the possibility that this transition would be adopted in clinical practice without involving the quarterly formulation.

Clinical inputs

The meta-analysis methodology has been described elsewhere [7]. In accordance with these methods and rationale, we conducted a literature search using MEDLINE/PubMed (last access May 20, 2022) with the aim to extract efficacy and effectiveness of LAIs and OAPs.

The search string was designed on the basis of the PICOS schema (Table II), as recommended by the PRISMA guidelines [10]. Further exclusion criteria included out-of-objective analyses, post hoc or subgroup analyses, and the unavailability of the full text.

Literature search and selection were conducted using the same criteria detailed in the previous paper [7]. The outcome was the hazard ratio (HR) of relapse between the two strategies. Therefore, as in the previous work, we selected all studies that compared two strategies differing in terms of active ingredient and/or administration route and/or inter-administration interval and extracted the adjusted HR from the text. When the outcome was not reported, we estimated it from the 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, whereas 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 HRs were pooled using a Bayesian statistical model, including the administration route and frequency. The effect of administration frequency on the risk of relapse, was modeled as proportional (HR depends on the ratio of frequencies), as this resulted the best approach in our previous analysis.

Economical inputs

The current and optimized scenarios were characterized by two cost chapters: drug acquisition costs and relapse management costs. Since the analysis was performed from the Italian NHS perspective, only direct costs were considered.

Regarding pharmaceutical costs, for all drugs, final prices did not vary between the two scenarios, except for monthly paliperidone, which had a lower price in the optimized scenario due to the recent launch of its generic formulation. To mimic the cost actually paid by the NHS, an average discount granted to hospital facilities was applied to the ex-factory price of each available package. The amount of this discount, which is 28.6%, emerged from a comprehensive analysis of drugs reimbursed by the Italian Medicines Agency (AIFA) in recent years [11]. Given that the negotiated discount for the transfer to facilities of a generic drug is

Administration frequency	Active substances	Average prices per active substance (hospital facilities) (€)	Average prices per administration frequency class (€)	
			Current scenario	Optimized scenario
Every 2 weeks	Risperidone	91.87	98.45	98.45
	Olanzapine	164.96		
Monthly	Olanzapine	211.36	213.12	181.05
	Risperidone	217.88		
	Aripiprazole	190.54		
	Paliperidone	Xeplion® 236.19 Off-patent 170.33		
Quarterly	Paliperidone	695.70	695.70	695.70
Semi-annual	Paliperidone	1,584.18	1,584.18	1,584.18

Table III. *Average prices per active substance and per administration frequency class*

Optimization movements	First switch (n.)	Second switch (n.)
From risperidone every 2 weeks to risperidone monthly	405	324
From risperidone every 2 weeks to paliperidone monthly	405	324
From paliperidone monthly to paliperidone quarterly	3,609	2,968
From paliperidone quarterly to paliperidone semi-annual	1,581	1,986
Total patients with optimized regimen as compared to the previously received one	5,998	5,601

Table IV. *Number of patients transited from shorter to longer dosing interval*

usually lower than that required for new medicinal entities, to simulate the price of generic paliperidone, a discount of two-thirds of the above-mentioned was applied.

The average price per active substance and per administration frequency class was then calculated on the basis of the market share of the different dosages reported by IQVIA for Italy for years 2018-2022 (Table III). The reduction from the current to the optimized scenario of the "monthly" class average price, shown in Table III, corresponds to the minimum difference between before and after the availability of the generic formulation; it does not capture the adding saving due to regional public tenders. However, this conservative approach was preferred.

The other chapter of expenditure, i.e., relapses management costs, was estimated for both scenarios by multiplying the events rate resulting from the updated meta-analysis for considered regimens by the cost incurred to manage the event. According to Expert opinion, the burden associated with a relapse generally included the entire management pathway, especially the hospitalization for the acute phase lasting an average of 10-15 days (quantified using regional tariffs) and the subsequent stay in residential facilities for rehabilitation for an average of 30 days: the resulting mean cost per episode was € 10,500 [7].

RESULTS

Consequences on ease of use

Patient flow defined a cohort of 49,398 patients receiving atypical LAI in Italy. Through the implementation of 6-month transition mechanism, the distribution of target patients among currently prescribed atypical LAI was modified twice a year from shorter to longer dosing intervals, leading to an overall optimization of the easy of therapy use.

As shown in Table IV, during the year of analysis, 11,600 patients experienced a quality-of-care improvement by reducing the time and resources spent managing their therapy. The resulting distribution among frequency classes in the two scenarios is presented in Figure 1, which clearly highlights the trend toward longer inter-dose interval regimens.

Clinical outcomes

The literature search identified 624 studies, plus 53 studies added through manual check, for a total of 677 studies. Of these, 419 studies were excluded after screening by title and ab-

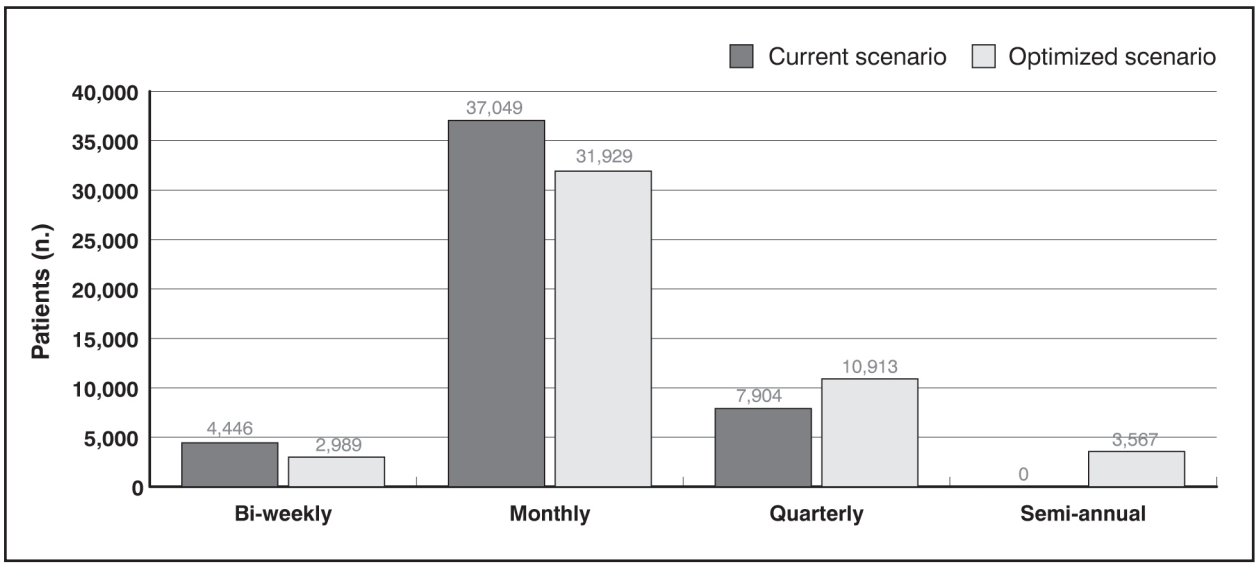

Figure 1. *Patients distribution among frequency classes in current and optimized scenarios (at the end of year, i.e. after the second switch)*

stract, and 258 were fully inspected. Finally, 50 studies (20 RCTs) met the inclusion criteria and were analyzed (Figure 2). The references list and the details of the studies included are presented in Tables S1 (all), S2 (RCTs), and S3 (observational studies) of the Supplemental material.

In general, the new results confirmed the previous ones: in the real-world setting, an atypical injectable drug reduced the risk of relapse by more than 30% (RR = 0.69, 95% CI: 0.66 to 0.71, credibility 100%) compared with the same active substance administered by the oral route. Furthermore, the risk of relapsing was reduced by 10% (RR =0.90, 95% CI: 0.81 to 0.99, credibility 98,3%) for each doubling of the inter-dose interval.

Table V shows the relative risks (vs. risperidone every 2 weeks, taken as reference) for all the atypical LAIs used in Italian clinical practice according to IQVIA 2018-2022 selling data. As can be seen, the relapse rate decreased with longer inter-administration intervals, and the

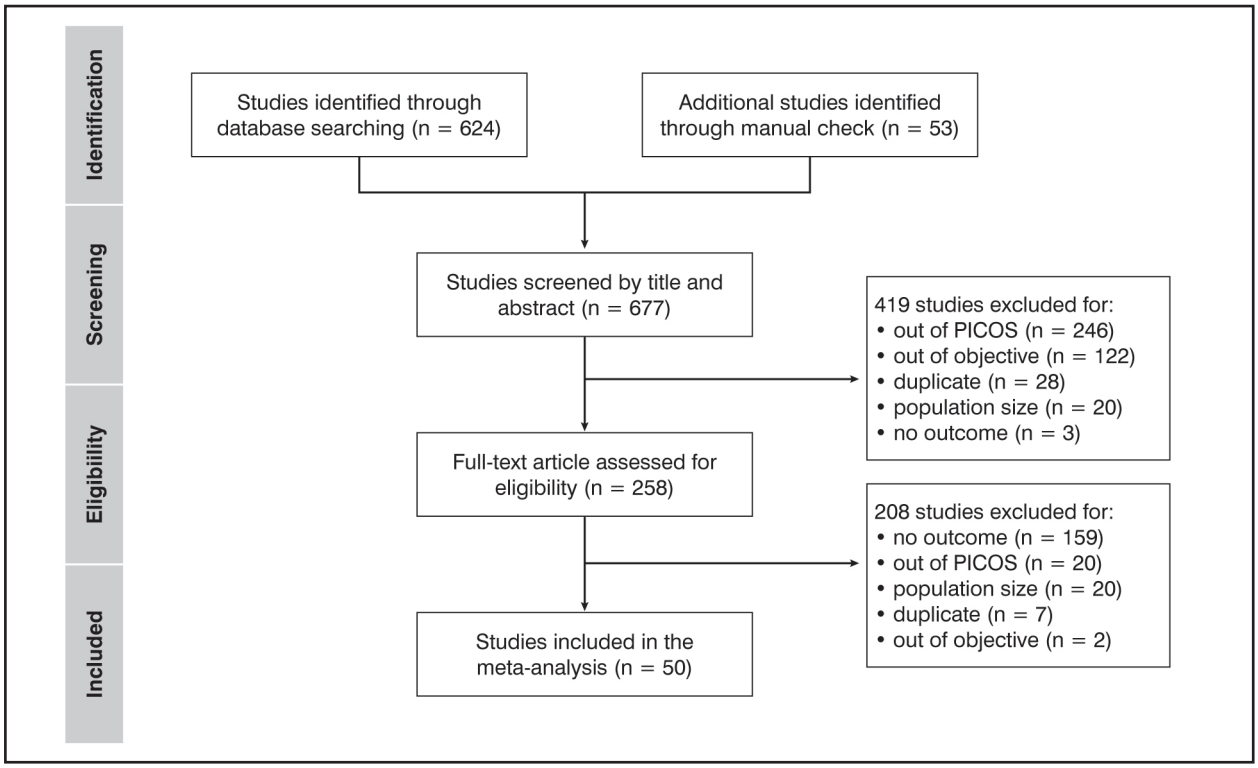

Figure 2. *Systematic review flow diagram*

Regimen	HR vs. RIS every 2 weeks	95% CI
Risperidone every 2 weeks	1.00	-
Olanzapine every 2 weeks	0.88	0.8 - 0.97
Olanzapine monthly	0.79	0.7 - 0.9
Aripiprazole monthly	0.91	0.77 - 1.08
Risperidone monthly	0.90	0.81 - 0.99
Paliperidone monthly	0.90	0.8 - 1.01
Paliperidone quarterly	0.60	0.37 - 0.93
Paliperidone semi-annual	0.35	0.1 - 0.89

Table V. *Hazard ratio of relapse vs. risperidone every 2 weeks in the real-world setting*
HR = hazard ratio; RIS = risperidone

Costs per strategies	Current scenario (€)	Optimized scenario (€)
Total	308,200,710	288,914,974
Every 2 weeks	28,958,268	21,725,175
Monthly	236,427,960	198,279,143
Quarterly	42,814,483	56,457,318
Semi-annual	-	12,453,338
Difference Optimized vs. Current	-19,285,737	

Table VI. *Costs per strategies in current e optimized scenarios*

Costs per resource type	Current scenario (€)	Optimized scenario (€)
Pharmaceutical expenditure	138,232,865 €	128,062,220 €
Difference optimized vs. current	- 10,170,645 €	
Relapses managing expenditure	169,967,845 €	160,852,753 €
Difference Optimized vs. Current	- 9,115,092 €	

Table VII. *Costs per resource type in current e optimized scenarios*

greatest reduction in the risk of relapse was expected with the use of SGA LAI administered once every 6 months, associated with an estimated reduction of 65% in the frequency of relapse, compared with the reference. Further results, referring to comparisons non-pertinent to the objective of the current analysis (typical antipsychotic, class of frequency global effect, etc.), are available in the Supplemental material (Table S4 and Figure S1).

To calculate the annual relapse rate associated with each drug considered in the analysis and, consequently, the management cost, HRs were applied to the baseline average incidence rate related to risperidone every 2 weeks (0.38 events/year).

Based on this elaboration, in the current scenario, patients experienced an average of 0,33 relapses in a year; the transition mechanism permitted the reduction of this rate of 5%, leading to almost 900 events being avoided every year.

Economic performance

The optimized scenario was associated with a lower total cost than the current one, with a cost saving of more than 19 million Euros; its distribution among strategies is shown in Table VI.

Savings were mainly driven by the reduction in the price of monthly paliperidone following the arrival of its generic formulation, leading to a lower pharmaceutical expenditure of at least 10 million Euros in one year (Table VII), considering that further discount for the hospital facilities supplied was neglected in the current analysis.

The other cost impact came from the transition toward strategies with a lower incidence of relapses and was subsequently associated with lower costs for their management: it amounted to slightly more than 9 million Euros (Table VI), representing almost 50% of the total savings.

DISCUSSION

Our network meta-analysis and its subsequent update aimed to explore the factors influencing the real-world efficacy of antipsychotics in relapse prevention. The findings indicate a significant increase in effectiveness with reduced administration frequency; for each additional week between doses, there is a 10% reduction in the risk of relapse. This dynamic is mainly due to the long-standing issue of poor adherence, which particularly characterizes daily or short-interval therapies, notably in challenging conditions such as mental illnesses.

Reinforcing this direction are the results emerging from another recent meta-analysis [12] that highlights the advantages of LAIs over daily OAPs across different study designs. LAIs have shown lower risks of hospitalization or relapse compared with oral drugs, with a substantial effect size in pre–post studies (risk ratio–RR = 0.44 [95% CI: 0.39 to 0.51]). In RCTs, as expected, effect sizes were smaller (RR = 0.88 [95% CI: 0.79 to 0.99]); this can be attributed to the fact that RCTs enroll more adherent patients, limiting the ability to highlight the benefits of LAIs. A peculiarity of this analysis is that cohort studies also present a small effect size (RR = 0.92 [95% CI: 0.88 to 0.98]), justified by the authors with the propensity of clinicians to prescribe LAIs to more severe patients.

In our NMA, LAIs demonstrated higher effectiveness than OAPs in real-world scenarios, including both cohort and pre-post studies. The hazard ratio of relapse versus the reference

(haloperidol as the least effective among OAPs) ranged from 0.81 (95% CI: 0.79 to 0.84]) for risperidone administered every 2 weeks to 0.21 (95% CI: 0.06 to 0.54]) for semi-annual paliperidone. The slight differences in the magnitude of the effect between the two meta-analyses might be due to different statistical approaches (network vs. standard, Bayesian vs. frequentist frameworks) and comparisons considered (individual LAIs vs. oral haloperidol as opposed to the general comparison between LAIs and OAPs) [12].

External validation could be achieved by comparing the rate attributed by our meta-analysis with the findings of the recently published open-label extension [13] of the semi-annual paliperidone pivotal trial [14]. A total of 178 patients who had received paliperidone, either quarterly or semi-annually, and had not experienced relapses during the previous blinded phase of the trial were enrolled to continue the open label observation, recording 7 relapses over a mean exposure time of 682 days. If the same 178 patients had entered our model and received semi-annual paliperidone from the first day of the year, they would have experienced 44 events. However, the difference may be easily explained by the fact that patients eligible for the open-label extension were clearly less likely to experience a relapse, because the eligibility criterion was not to have experienced any event during the previous 12-month blinded phase.

Using the meta-analysis results for the economic evaluation, we estimated that the cost for the management of Italian patients in treatment with LAIs amounts to approximately 300 million Euros per year, including both drug acquisition and relapse management costs. To assess the reliability of our estimate, it would be interesting to compare it with the findings of cost-of-illness studies. Therefore, the expenditure for the management of almost 200,000 Italian patients receiving OAPs has been estimated. The average monthly pharmaceutical cost per patient of an OAP, based on the Italian wholesale mix recorded by IQVIA for the period 2018-2022 and applying a 50% adherence rate, is € 15. If only pharmaceutical expenditure is considered, oral therapies would appear to be cheaper but are also associated with a higher risk of relapse, as found in our NMA where a hazard ratio OAP vs. risperidone of 1.41 emerged. Therefore, considering the costs for relapse management, the total expenditure for the management of orally treated patients amounts to about € 1.14 billion per year, which is added to the total expenditure for patients treated with LAIs previously reported.

A local cost-of-illness (COI) study estimated, using a probabilistic model, a total cost of € 1.37 billion per year incurred by the NHS for the management of schizophrenia [9], aligning consistently with our findings, considering that the COI's estimate referred to 2014.

With the dual opportunity to reduce the economic impact of schizophrenia on the NHS by reducing both pharmaceutical and relapse management costs and to alleviate the burden of the condition on patients, by improving adherence and subsequent relapse onset, the transition to therapies with longer inter-dose intervals is a simple and cost-effective approach to optimize the treatment of schizophrenia.

Our simulation estimates that the implementation twice a year of a 20% transition rate to the next optimized therapy avoids 900 relapses per year and saves more than 19 million Euros.

It would be crucial that this saving should not remain an *end in itself*, but be retained within Mental Health and used as fuel to initiate a virtuous cycle to optimize the health outcomes of other patients.

One way forward in this direction could be to reinvest the generated savings to finance and facilitate the transition of an increasing number of patients from daily oral therapies to LAIs.

A challenging exercise might be calculating the number of patients taking OAPs who can be transitioned to LAIs using accrued savings.

The average cost of an OAP-to-LAI switch is about 500 Euros as a result of the higher pharmaceutical costs of injectable drugs compared with oral ones (about 2,200 Euros), partially offset by the lower costs for relapse management (about 1,700 Euros).

This elaboration shows that, thanks to the reinvestment of the accrued savings, approximately 38,600 patients could shift from a daily oral to a long-acting injectable regimen, at no adjunctive cost for the NHS.

These results come from a conservative approach that considers an adherence rate of 50% for OAPs and 100% for LAIs. If the adherence factor was removed from the calculation, the transition funded by reinvestment would rise to almost 60,000 patients.

We believe that the strength of this analysis lies in the reliability of the clinical estimates: the analyzed data confirm the hypothesized relationship between administration frequency and risk of relapse, a relation presumably driven by adherence as the main factor. Therefore, we consider the estimated savings to be a realistic result achievable by the health service if the prescribing system follows the hypothesized dynamics. Similarly, the

balance between reinvestment and optimization is transparent and linear, anchored to real-world data.

The main limitation of our analysis is that we did not examine whether the effectiveness data associated with LAI were obtained in settings that have adopted an organized recall service for scheduled visits to receive the injectable therapy, thus promoting adherence. However, the implementation and dissemination of such a digital technology would likely be associated with a negligible cost when compared with the estimated savings.

CONCLUSION

Optimizing the treatment of patients with schizophrenia using therapies with extended dosing intervals, which are therefore less likely to induce nonadherence, can have significant clinical, organizational, and economic benefits; the reinvestment of the saving resulting from the optimization may finance the transition of additional patients from daily oral therapy to LAI formulations, thus initiating a virtuous process.

Funding

The study was made possible by an unconditional grant from Johnson&Johnson.

Conflicts of interest

OZ and MP are employees of AdRes, which has received project funding by Johnson&Johnson for the conduct of the study.
SM is employee of Johnson&Johnson.
LP is co-owner and employee of AdRes, which has received project funding by Johnson&Johnson for the conduct of the study.

REFERENCES

1. Velligan DI, Wang M, Diamond P et al. Relationships among subjective and objective measures of adherence to oral antipsychotic medications. *Psychiatr Serv*. 2007;58:1187-92; https://doi.org/10.1176/ps.2007.58.9.1187
2. Valenstein M, Ganoczy D, McCarthy JF, Myra Kim H, Lee TA, Blow FC. Antipsychotic adherence over time among patients receiving treatment for schizophrenia: a retrospective review. *J Clin Psychiatry*. 2006;67:1542-50; https://doi.org/10.4088/jcp.v67n1008
3. Lieberman JA, Stroup TS, McEvoy JP, et al. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353:1209-23; https://doi.org/10.1056/NEJMoa051688
4. Milz R, Benson C, Knight K, et al. The Effect of Longer Dosing Intervals for Long-Acting Injectable Antipsychotics on Outcomes in Schizophrenia. *Neuropsychiatr Dis Treat*. 2023;19:531-45; https://doi.org/10.2147/NDT.S395383
5. Kishimoto T, Robenzadeh A, Leucht C, et al. Long-acting injectable vs oral antipsychotics for relapse prevention in schizophrenia: a meta-analysis of randomized trials. *Schizophr Bull*. 2014;40(1):192-213; https://doi.org/10.1093/schbul/sbs150
6. Kishimoto T, Nitta M, Borenstein M, Kane JM, Correll CU. Long-acting injectable versus oral antipsychotics in schizophrenia: a systematic review and meta-analysis of mirror-image studies. *J Clin Psychiatry*. 2013;74:957-65; https://doi.org/10.4088/JCP.13r08440
7. Zaniolo O, Ghetti G, Povero M, Pradelli L. Effectiveness of Long-Acting Injectable Antipsychotics in Schizophrenia: A Literature Review and Bayesian Meta-Analysis Informing Economic Considerations. *Farmeconomia. Health economics and therapeutic pathways*. 2019;20(1):13-24; https://doi.org/10.7175/fe.v20i1.1393
8. ISTAT 2022 popolazione residente al 1° gennaio 2022. Available at https://demo.istat.it/ (last accessed April 2024)
9. Marcellusi A, Fabiano G, Viti R, et al. Economic burden of schizophrenia in Italy: a probabilistic cost of illness analysis. *BMJ Open*. 2018;8(2):e018359; https://doi.org/10.1136/bmjopen-2017-018359

10. Moher D, Liberati A, Tetzlaff J, et al.; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-12; https://doi.org/10.1016/j.jclinepi.2009.06.005

11. Villa F, Tutone M, Altamura G, et al. Determinants of price negotiations for new drugs. The experience of the Italian Medicines Agency. *Health Policy*. 2019;123(6):595-600; https://doi.org/10.1016/j.healthpol.2019.03.009

12. Kishimoto T, Hagi K, Kurokawa S, Kane JM, Correll CU. Long-acting injectable versus oral antipsychotics for the maintenance treatment of schizophrenia: a systematic review and comparative meta-analysis of randomised, cohort, and pre-post studies. *Lancet Psychiatry*. 2021;8(5):387-404; https://doi.org/10.1016/S2215-0366(21)00039-0

13. Najarian D, Turkoz I, Knight RK, et al. Long-Term Efficacy and Safety of Paliperidone 6-Month Formulation: An Open-Label 2-Year Extension of a 1-Year Double-Blind Study in Adult Participants With Schizophrenia. *Int J Neuropsychopharmacol*. 2023;26(8):537-44; https://doi.org/10.1093/ijnp/pyad028

14. Najarian D, Sanga P, Wang S, et al. A Randomized, Double-Blind, Multicenter, Noninferiority Study Comparing Paliperidone Palmitate 6-Month Versus the 3-Month Long-Acting Injectable in Patients With Schizophrenia. *Int J Neuropsychopharmacol*. 2022;25(3):238-51; https://doi.org/10.1093/ijnp/pyab071