

The impact of the ambiguous definition of “month” on pharmacotherapy

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ABSTRACT

Aim: The Gregorian calendar divides a common year into 12 months of irregular length. As a result, whenever time is measured in months, an unavoidable degree of inaccuracy exists. We hypothesize that the use of this unprecise measure of time has profound implications for the field of pharmacotherapy from practical and drug safety issues, to variations in drug budgets, and pharmacoepidemiological, industrial and drug regulatory considerations, such as price-fixing policies. In this paper, we have tried to gather evidence in favor of our hypothesis, focusing on the particular case of antipsychotics.

Methods: First, we examined all monthly prescriptions of long acting injectable aripiprazole or paliperidone in the Basque Country from January 1st to December 31st, 2017. Second, we investigated how the WHO Collaborating Centre for Drug Statistics defines the defined daily dose (DDD) for these drugs. Third, we analyzed the pack size of oral solid formulations of antipsychotics on the market in Spain. Finally, we explored how evidence from clinical trials is transferred to clinical practice and how it may affect drug fixing-policies.

Results: We found that “monthly” and “every 4 week” injections were prescribed for approximately half of patients. We estimated that an extra cost of almost half a million euros (€495,420) would have been incurred if all prescriptions had been every 4 weeks. We also found that 21 additional adverse site reactions per year could be expected for aripiprazole.

Besides, the WHO Collaborating Centre for Drug Statistics calculates the defined daily dose using a 30-day interval for these drugs.

In addition, we found that pack sizes for currently available solid oral antipsychotic formulations are inconsistent, with 53% being sold as 28-day multiples and 46% as 30-day multiples.

Finally, we found out that although the vast majority of clinical trials are performed in weeks, drug regulatory agencies frequently use the term “month” or “monthly” in the summary of product characteristics of marketed antipsychotics.

Conclusion: This study shows that the inconsistent definition of month has deep implications on various aspects of pharmacotherapy. Considering all the data given above, we urge drug regulatory agencies to specifically avoid the term “month” in the summary of product characteristics and adopt 4-week intervals instead. We also suggest that the WHO Collaborating Centre for Drug Statistics establishes a new 28-day based DDD for “monthly” antipsychotics. Finally, healthcare providers worldwide should abstain from using “monthly” frequencies in drug prescription software tools.

Introduction

Humans have measured the passing of time since ancient times with increasing accuracy. Nowadays, the second, the International System of Units base unit of time, is defined in incredibly precise terms as: “9,192,631,770 times the period of the radiation corresponding to the transition between the two hyperfine levels of the ground state of the

caesium-133 atom” [1].

A month is far more difficult to define in precise physical terms. According to the Encyclopaedia Britannica, a month is a “measure of time corresponding or nearly corresponding to the length of time required by the Moon to revolve once around the Earth” [2]. Therefore, as a calendrical period, the month is derived from the time elapsing between successive new moons or other phases of the moon (lunation or synodic month). A

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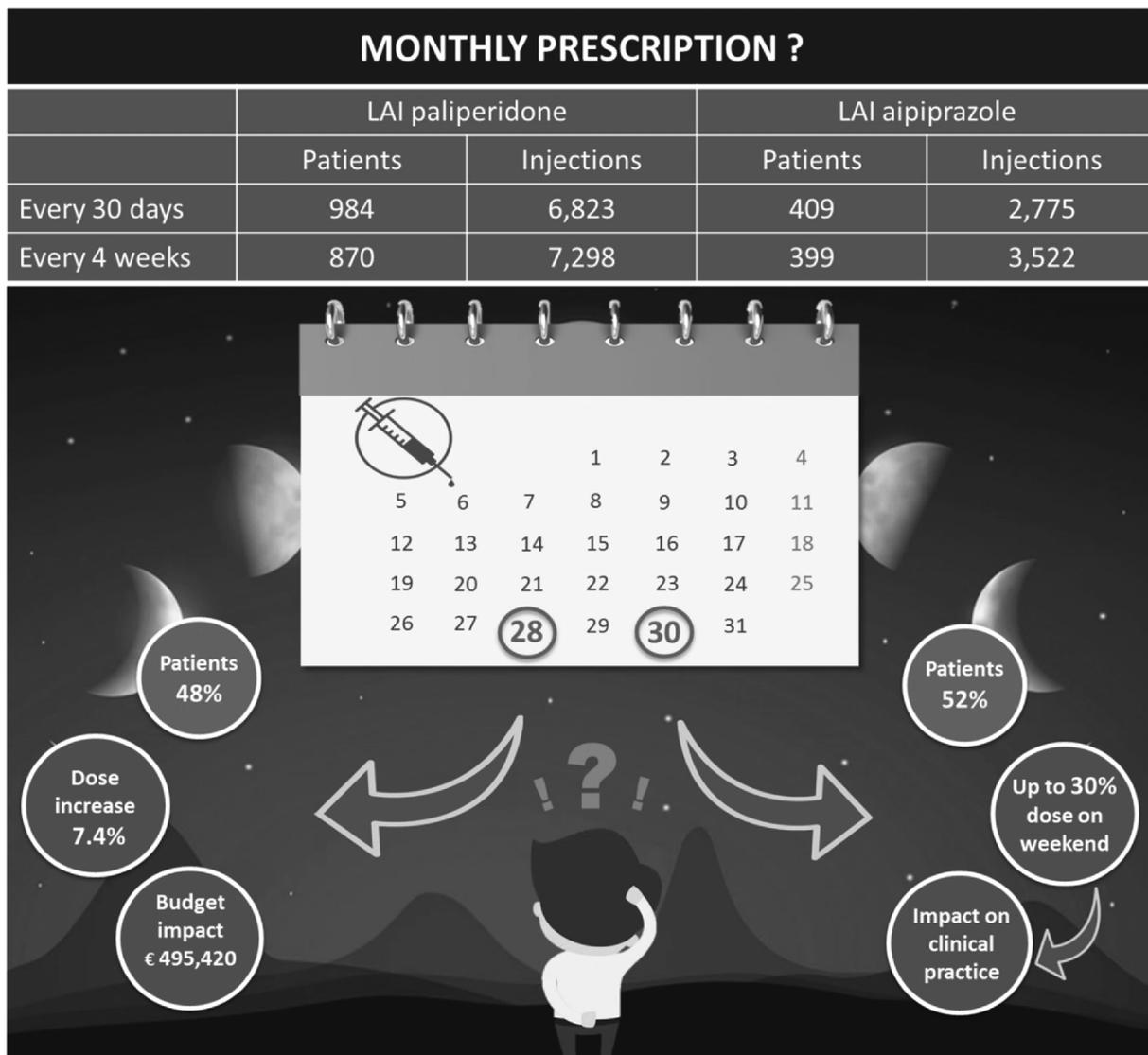


Fig. 1. Monthly prescription of long acting injectable aripiprazole and paliperidone (LAI) in the Basque Country.

total of 12 lunations amounts to 354 days, that is, very roughly a year. Therefore, some arrangements are required to adjust the measurement of time based on lunar phases to the actual (solar) duration of a year. Some calendars added epagomenal, intercalary days outside any regular month, whereas others, like the Roman calendar, attempted to synchronize lunar and solar systems with leap months. Another strategy is that of the Gregorian calendar, the solar-based system now in general use, created thanks to the astronomers working at the University of Salamanca in the 16th Century [3]. Approved by Pope Gregory XIII in a bull more than four centuries ago, it divides a common year into 12 months of irregular length. As a result, months are no longer linked to the phase of the Moon, but are based on the motion of the Sun relative to the equinoxes and solstices, the consequence being months with 28, 30, or 31 days during a common year, plus a 29-day February in leap years. So, whenever time is measured in months, an unavoidable degree of inaccuracy exists. This is the reason why in situations where a high degree of accuracy is essential, like pregnancies, time is measured in weeks rather than months. However, the term “month” is still frequently used in many other areas in healthcare, such as pharmacotherapy. As far as we are concerned, little attention has been given to the potential impact of the use of this unprecise term on drug therapy. In this study we will focus on the particular case of long acting injectable antipsychotics (LAI).

Hypothesis

We hypothesize that the use of the ambiguous term “month”, derived from the Gregorian calendar, has profound implications for the field of pharmacotherapy, from practical and drug safety issues to variation in drug budgets and pharmacoepidemiological, industrial and drug regulatory considerations, such as price-fixing policies.

Discussion

The case of long acting injectable (LAI) antipsychotics

Together with clozapine, long-acting injectable (LAI) or depot antipsychotics are the most effective treatments for preventing not only psychiatric, but all-cause hospitalization among patients with schizophrenia [4]. In recent years, several LAI compounds have been approved for “monthly” administration, making that approach common in routine clinical practice. But given that a month is not an invariable length of time, “monthly” drug prescription can entail certain problems. First, intervals between injections may differ, with longer gaps between, say, doses administered in January and February, and shorter ones between those administered in February and March. Further, a monthly interval implies that injections will sometimes have to be

Table 1
Pack size of oral solid formulations of antipsychotics on the market in Spain.

	28-day multiple	30-day multiple	Other	Total
Amisulpride	0	31	0	31
Aripiprazole	117	0	0	117
Asenapine	0	2	0	2
Chlorpromazine	0	1	1	2
Clotiapine	0	1	0	1
Clozapine	0	0	8	8
Haloperidol	0	2	0	2
Olanzapine	308	0	0	308
Paliperidone	6	0	0	6
Perphenazine	0	0	1	1
Periciazine	0	1	1	2
Pimozide	0	2	0	2
Quetiapine	0	229	0	229
Risperidone	48	123	0	171
Sertindole	3	1	0	4
Sulpiride	0	4	1	5
Ziprasidone	35	0	0	35
Zuchlopentixole	0	2	1	3
Total	517 (56%)	399 (43%)	13	929

administered on weekends, involving problems of accessibility to services. Some prescribers opt for four-weekly injections on business days, but this decision, besides generating variability between practices and practitioners, may not comply with the specifications in the summary of product characteristics (SPC) of each compound.

A look at current prescription habits can exemplify the real-world consequences of using “monthly” intervals in pharmacotherapy. To that end, we extracted information on prescriptions from PRESBIDE, the prescription software tool used in the Basque Country, an autonomous region in northern Spain, with a population of around 2 million people, where Osakidetza, the region’s public health service, is the main mental health provider. PRESBIDE lists the pharmacological treatment history of each patient, sets the frequency at which a given drug can be supplied by a retail pharmacy, and offers information on adherence (estimated from prescriptions collected by patients from pharmacies) that can be exploited for administrative purposes. We examined all (anonymized) prescriptions of LAI aripiprazole or LAI paliperidone during one year: from January 1st to December 31st, 2017. As we focused on compounds intended for “monthly” administration, 3-monthly paliperidone was excluded. In PRESBIDE, any drug can be prescribed at roughly monthly intervals in two different ways. The program allows for “monthly” prescriptions, where a “month” is considered as a 30-day interval. Alternatively, the physician can choose “other frequencies” and specify a 28-day, or even a 4-week, interval between injections (resulting in one injection every 4 weeks = q4w). Neither Gregorian calendar 31-day months, nor other month definitions such as sidereal, synodic, tropical, anomalistic, draconic, or calendar months were considered as they are not included in PRESBIDE’s predetermined prescription intervals. This study was approved by the Clinical Research Ethics Committee of the Basque Country.

The results of our study are summarized on Fig. 1. We identified some depot aripiprazole or depot paliperidone prescriptions in 2534 different patients during the study period, accounting for a total of 21,952 injections dispensed. We discarded a subset of 1534 prescriptions with intervals other than monthly or q4w, and hence, only 20,418 injections dispensed were finally considered in the analysis, with 805 patients on LAI aripiprazole and 1772 patients on LAI paliperidone. Importantly, 36 patients were switched from one LAI antipsychotic to the other at some point in the study period, that is, they were treated with both products in the course of 2017.

As shown in Fig. 1, “monthly” and q4w injections frequencies were prescribed for approximately half of patients for each LAI antipsychotic.

Practical considerations

Currently, although “monthly” prescribed in PRESBIDE (i.e., intended for 30-day administration intervals), injections are very likely administered q4w to avoid injection dates on Saturdays or Sundays. As PRESBIDE calculates the number of doses allowed according to the dosage established by the prescriber for a maximum of a year, patients on 30-day prescriptions who are in fact on q4w regimes will need 13 doses over the course of a year while they have been prescribed just 12. The supplementary injection may be missing as the pharmacist is not allowed to supply doses not prescribed in PRESBIDE.

If these “extra” trips to the pharmacy lead to non-adherence and subsequent relapse in schizophrenic patients, should be a matter of further research.

Safety considerations

Assuming that monthly administration as recommended by SPCs is the correct way to use a LAI, any q4w regime entails an extra 7% dosage and one extra dose per year with respect to monthly (30-day) ones, and this could involve a higher risk of side effects, including injection site reactions. Regarding LAI aripiprazole, for which the SPC indicates a 5.1% incidence of injection site pain/induration, we should expect as many as 21 additional events per year.

Budget impact

An extra cost of almost half a million euros (€495,420) would have been incurred if all prescriptions had been q4w according to our data (€129,035 for aripiprazole and €366,385 for paliperidone).

Pack size of solid oral antipsychotics sold in Spain

Tablets or capsules containing marketed drugs are commonly prepared for “monthly” time intervals. We found that the imprecise definition of month affects the available pack sizes of antipsychotics. As shown in Table 1, approximately half of antipsychotics on the market in Spain are available as multiples of 28 while the other half are available as multiples of 30. This fact reflects the different interpretation of the term “month” adopted by different drug manufacturers.

Pharmacoepidemiological, industrial and drug regulatory considerations

The uncertain length of a month also affects pharmacoepidemiological indicators and may have profound implications for drug regulation and pharmaceutical industry.

Defined daily dose

The defined daily dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults. Only one DDD is assigned per ATC code (active principle) and route of administration (e.g., intramuscular). DDDs are very useful as a fixed unit of measurement independent of price, currencies, pack size and strength, enabling researchers to assess trends in drug consumption and perform comparisons between population groups.

Our findings show that for LAI antipsychotics approved for once-monthly administration, the DDD is defined using a 30-day interval (e.g., DDD = 400 mg/30 days for aripiprazole) [5]. If, however, these drugs are administered q4w, a 30-day DDD underestimates real consumption by about 7%. Furthermore, an actual q4w administration could have a dramatic impact on drug regulatory issues such as price-fixing policies. Given the tendency to administer “one-monthly” LAIs on a q4w basis, it would be more realistic to calculate their DDDs using a 28-day interval.

Drug regulatory and price-fixing policies

The SPC of both LAI paliperidone and LAI aripiprazole state that they must be administered “once-monthly” [6,7], even though in most pivotal studies both compounds were injected q4w [8–11]. Additionally, one-monthly paliperidone palmitate was compared to q2w (twice in a month) depot risperidone in a monograph published in Spain by Janssen [12] (manufacturer and patient holder of both compounds), highlighting that the former cuts costs by €217.5. To this, we should also add to further savings of €337.3, as the number of injections required is reduced by more than 50%. A critical, independent review offered a nuanced perspective, noting that such savings can only be appreciated in the second year of treatment, given that using depot paliperidone implies additional injections during the first year [13]. Nonetheless, q4w administration of LAI paliperidone, frequent in clinical practice and in clinical trials, involves a small extra cost of €44.2 as compared to LAI risperidone.

Therefore, it could be suspected that turning clinical trial q4w injections into recommendations for monthly administration might involve a promotional strategy, but the issue is more complex. In this sense, Aristada™ (aripiprazole lauroxil, not available in Europe) has obtained FDA approval in four doses and three prescription intervals for the treatment of schizophrenia (441 mg, 662 mg or 882 mg monthly, 882 mg every six weeks and 1064 mg every two months) [14]. It is difficult to know why both the FDA and the manufacturer use a mixture of weeks and months to set injection intervals.

Moreover, while we were writing this paper, it has been reported that the first subcutaneous depot antipsychotic, containing the active ingredient risperidone, has obtained FDA approval and will be marketed under the name Perseris™. Despite clinical trials involved a four week administration interval [15] (90 mg and 120 mg injections were administered on days 1 and 29) the product’s factsheet describes a “monthly” dosing interval [16].

A similar inconsistency can also be seen in the case of “3-monthly” paliperidone palmitate, which was actually administered every 12 weeks in clinical trials [17]. The discrepancy allows for a cumulative delay of as much as 7 days for each injection. Certainly, the SPC’s missed dose section allows for a margin of 2 weeks before or after the 3-month time point that would compensate sufficiently for the delay [18], but in the long run, a systematic, 1-week mismatch between clinical trial protocols and SPC-recommended practice may contribute to a reduction in effectiveness.

On the contrary, trials comparing 3-monthly with a new half-yearly LAI paliperidone are designed to be administered at exactly 182 day intervals, with sham injections fixed at near 3-monthly intervals (on days 92 and 274) [19]. Accordingly, if the new compound becomes available, clinicians setting the date for the following injection will only need to deal with one epagomenal day (two, in leap years), even though the problem with weekend injections will remain.

In summary, although the vast majority of clinical trials are performed in weeks, drug regulatory agencies frequently allow the use of the term “month” or “monthly” in the summary of product characteristics of marketed antipsychotics.

Conclusion

We have showed that the imprecise term “month”, derived from the solar Gregorian calendar, has deep consequences on the field of pharmacotherapy, including practical and drug safety issues, variations in drug budgets, and pharmacoepidemiological, industrial and drug regulatory considerations, such as price-fixing policies. Therefore, we urge drug regulatory agencies to specifically avoid the term “month” or “monthly” in the dosage information in the SPCs not only for depot antipsychotics, but for all other drugs in general, and use week intervals instead, in line with the clinical trials which provided the evidence for

their approval.

We also suggest that the WHO Collaborating Centre for Drug Statistics establishes a new 28-day based DDD for “monthly” drugs, so that there are comparable measuring instruments for all available products. Finally, we also consider that healthcare providers worldwide should abstain from using “monthly” frequencies in electronic drug prescription software tools.

In the meantime, it is somewhat difficult to dispel the suspicion that when using the term “month” in pharmacotherapy, we are “*measuring it with a micrometer, marking it with a chalk, and cutting it with an axe*”.

Declaration of Competing Interest

The authors declare no conflicts of interest

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2019.109258>.

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