Medication non-**A**dherence from **P**hysicians' **P**erspective:

MAPP Study Protocol

V 26072016

Stéphanie SIDORKIEWICZ [1, 2] stephanie.sidorkiewicz@parisdescartes.fr

Viet-Thi TRAN [2] thi.tran-viet@htd.aphp.fr

Philippe RAVAUD [2,3,4] philippe.ravaud@htd.aphp.fr

[1] Department of General Medicine, Paris Descartes University, Paris, France

[2] METHODS Team, Epidemiology and Statistics Sorbonne Paris Cité Research Centre, UMR 1153, INSERM, Paris, France

[3] Cochrane France

[4] Department of Epidemiology, Mailman School of Public Health, Columbia University, New York City, United States of America

Introduction

Medication adherence is defined as the extent to which a person's behavior coincides with medical advice.(1) Studies have shown that approximately 50% of patients stop taking their medications 6 months after initiation. (1, 2) When patients stop taking their medications, drug actions fade, as summed up by the US surgeon C. Everett Koop saying: "Drugs don't work in patients who don't take them". The association between drug non-adherence and clinical outcomes is well known in the literature (3), but most studies considered adherence solely as the ratio of doses taken and the number of doses prescribed without taking into account the different drugs patients may have or the different adherence behaviors the may exhibit.

1.1 Medication adherence as a dynamic process

In the literature, adherence is often defined as a percentage of taken doses on the total number of prescribed doses. Usual threshold used to define "good adherence" is a patient taking >80% of all prescribed doses. This threshold may be different for specific treatments: for example, a patient is considered adherent for antiretroviral treatments only if he takes >95% of prescribed doses (1, 4).

However, medication adherence cannot be simply summarized as a rate of drug intakes. It is a complex and dynamic process where patients adhere differently to their multiple drugs and exhibit various medication-taking behaviors (as drug holidays, missing doses or schedule errors) (5, 6). A taxonomy published by Vrijens et al. describes adherence as a process divided into three phases (7). First, a patient starts to take the first dose: it is the *initiation*. Second, the patient continues to take the treatment: the extent to which dosing corresponds to the prescribed dosing regimen defines the *implementation*. Third, the patient may stop the treatment: the end of the therapy defines the *discontinuation*. Finally, *persistence* is defined as the length of time between initiation and discontinuation.

1.2 Clinical consequences of poor implementation

The risk of adverse events due to poor implementation varies according to: the drug concerned, the disease being treated, the length of drug interruption or the frequency of missed doses.

Adverse events caused by imperfect medication intakes may range from minor symptoms to suboptimal clinical benefit (8), poor control of the illness (9), emergence of treatment-resistance (10) or life-threatening event (11). The seriousness of these adverse events depends on the patient health status, the drug and the disease being treated. For example, in transplantation therapy, even minor deviation of optimal adherence to immunosuppressive treatment can lead to severe consequences (12).

In the literature, studies on consequences of non-adherence have described the potential adverse events which may occur due to poor adherence (for example risk of stroke and major bleeding among patients with atrial fibrillation taking anticoagulants (11) or graft loss and mortality after kidney transplantation (12)). In these studies, threshold for non-adherence was a patient taking <80% of prescribed doses. Only few studies have tried to assess an acceptable cut-off for "good adherence" (13, 14). However, these studies used to define this cut-off as drug intake rate (15) such as the proportion of days covered (PDC) or medication possession ration (MPR). As of today, the effects of specific medicine-taking behaviors (drug holidays or episodic drug omissions) are not accurately known. To the best of our knowledge, there is no accurate description of the consequences of these precise behaviors in any treatment context. Providing these data could contribute to build a "global risk mapping" of medication non-adherence behaviors.

1.3 The concept of forgiveness

A first approach to solve this issue and to take into account the effects of medicine-taking behaviors could be to consider drugs' forgiveness. Drug forgiveness (F) is the difference between the medication's post dose duration of beneficial action (D) and the prescribed dosing interval (I): $F=D-I$ (5). Drug forgiveness depends on pharmacokinetic and pharmacodynamics of the drug. However, estimation of drug forgiveness is difficult and involves either "placebo-substitution-for-active" (16) which are limited for ethical reasons (5)

or complex models based on pharmacokinetic and pharmacodynamics properties of the drugs (17). In addition, if drug forgiveness evaluates the short-term risk of adverse events due to poor implementation of a given drug, it does not take into account the seriousness of the potential adverse event, nor the long-term consequences of poor adherence (e.g. poor control of the illness).

1.4 How much adherence is enough?

For patients with multiple medications, perfect drug adherence (all doses taken at the correct time, during their whole lives) may be unrealistic (18). Therefore, clinicians facing patients with various medication-taking behaviors have to assess how much non-adherence is acceptable to achieve desired therapeutic effects (19) without unnecessarily increase the patient's burden of treatment.

In this study, we propose to focus on the level of non-adherence acceptable by physicians. We hypothesize that physicians' clinical experience will allow them to integrate the different aspects involved (the risk of an adverse event occurring, the seriousness of the potential adverse event, the timeline for the occurrence of the event, the disease being treated, patient's burden of treatment, and time needed for intervention to improve patient adherence) in their decision.

2. Objective

Our aim is to assess the acceptable non-adherence threshold, according to physicians, for a large number of different long-term treatments.

3. Methods

The MAAPP study is a survey among physicians about the acceptable non-adherence threshold for different long-term treatments. Each participating physicians will contribute to the study by evaluating a small number of medications. From all answers, we will determine the acceptable non-adherence thresholds for a large number of medications.
The study involves 3 steps: 1) development of the survey; 2) identification of the medications that will be assessed; and 3) data collection and analysis.

3.1 Step 1: Development of the survey

Our survey is intended to assess the acceptability of different non-adherence behaviors and their magnitude, according to physicians, for a large number of medications and conditions.

1. *Literature search*

We first searched the literature to theoretically conceptualize the content of the questionnaire. This search aimed to:

1) Define the medication non-adherence behaviors assessed in the study
2) Adapt the wording of the introductory sentences and the clinical vignettes of the questionnaire

2. *Draft of a preliminary version of the questionnaire*

In the literature, we identified various medication-taking behaviors as drug holidays, missing doses or schedule errors (1, 5, 6). We chose to focus on 1) drug holidays and 2) missing doses.

A working group composed of two general practitioners (SS and V-TT) and a professor of epidemiology (PR) elaborated a preliminary survey under the form of clinical vignettes presenting a standard patient taking a given medication in a given condition. The clinical vignette was followed by two questions assessing: 1) the threshold for inacceptable risk for varying frequency of drug omissions, and 2) the threshold for inacceptable risk for varying drug holidays length.

Questions were inspired from both: 1) studies describing consequences of medication adherence, globally (15) and in specific medical areas (3, 9, 11, 12, 20-23); and 2) studies on how to communicate risk (24-26) and risk assessment (27-29).

We devised the survey so that each physician participating in the study would answer 10 clinical vignettes for drugs and conditions related to his medical specialty (see below).

3. *Pilot testing of the questionnaire*

Clarity and understanding of the questions were during a first pilot-testing with 4 physicians using the double interview method. In the double interview, researchers ask participants to answer the question and then explain why they chose a particular answer. Discrepancies between what was intended and what was understood by participants will be noted to adapt the wording (30). We took into account all their comments and modified the preliminary content of the website.

Resulting questions of the web-based survey tool are detailed in Appendix.

4. *Technical development of the internet platform*

Our study will be conducted online using a dedicated website. We adopted an approach inspired by crowd sourcing platforms (31) to allow assessment of a large number of medications. Each participant will be invited to complete the survey and assess 10 clinical vignettes, representing 10 "medication/indication" situations (a specific drug in a given therapeutic indication) randomly selected in the database. We chose this approach because it was not feasible to ask participants to rate all possible drugs.

The technical procedure will be tested before the survey.
The internet platform will be designed by a web designer.

3.2 Step2: Identification of the medications that will be assessed

In this study, we intend to assess a large number of medications commonly taken by patients. To determine the medications that will be assessed, we used the list of medications reimbursed by the National Insurance System in France during the first semester 2015. One investigator (SS) grouped medications by pharmaceutical substance, as named in the International non-proprietary naming (INN) convention.
One example is detailed in Figure 2.

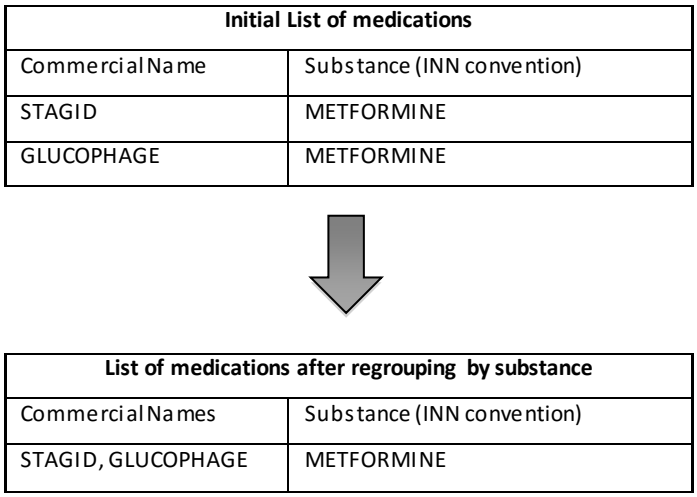


Figure 2. Medications regrouping process

Two investigators (VT-T, SS), then independently excluded:

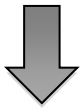
- Medications prescribed less than daily
- Medications prescribed only for acute or pediatric conditions
- Medications for diagnostic purpose
- Vaccinations, electrolyte solutions, antiseptics

Discordance between their decisions was resolved by consensus.

We kept in the database medications for which more than 100000 pillboxes had been reimbursed during the first semester 2015.

For each medication in the list, one investigator (SS) searched the French Vidal Dictionary for the corresponding therapeutic indication(s) and usual daily dosage. When several indications or recommended dosages were proposed, we created multiple corresponding rows.

List of medications after regrouping by substance	
Commercial Names	Substance (INN convention)
STAGID, GLUCOPHAGE	METFORMINE
AVLOCARDYL	PROPANOLOL



List of medications assigned to corresponding therapeutic indications		
Commercial Names	Substance (INN convention)	Medical Indication
STAGID, GLUCOPHAGE	METFORMINE	Diabetes treatment
AVLOCARDYL	PROPANOLOL	Long-term treatment after myocardial infarction
AVLOCARDYL	PROPANOLOL	High blood pressure treatment
AVLOCARDYL	PROPANOLOL	Migraine long-term treatment
AVLOCARDYL	PROPANOLOL	Supraventricular rhythm disorders treatment

Figure 3. Therapeutic indications assignment process

Finally, we created sub-lists of medications relevant to the different medical specialties. In the database from the National Insurance System in France, there is the information on the medications most prescribed by ambulatory specialists. From this information, we devised specialty lists consisting of the 40 medications most prescribed (in terms on number of pillboxes) in ambulatory specialists. For general practitioners, we considered the 200 most prescribed medications. In case a medical specialty was not represented in the data from the National Insurance System (e.g. they only work in hospitals), one investigator (SS) assigned 40 medications to them.

3.3 Step 3: Data collection

1. *Participants*

Participants will be physicians, with an access to internet and understanding French Language.

We will exclude medical students, residents, and retired physicians or pharmacists.

Participants will be approached by various ways: university networks, hospital networks social networks, congresses. Physicians who have participated in the study will be encouraged to invite colleagues to participate (snowball sampling).

Participants will be informed about data analysis respecting confidentiality. The study website has been declared to the French Data Protection Authority (CNIL).

2. *Web-based survey tool*

Participants' characteristics

We will collect basic demographic information (age, sex, country) and professional information (medical specialty, ambulatory or hospital practice setting).

10-clinical vignettes questionnaire

Then, participants will complete 10 clinical vignettes (corresponding to a specific drug in a given therapeutic indication) randomly selected from the list of medications corresponding to their specialty. If they already assessed all medications from their specialty, they will assess a random medication from the database, which they did not previously assess. For each medication we will collect information on: 1) their estimation of the frequency of drug omission which may put the patient at inacceptable risk; and 2) their estimation of the duration of a drug holiday that may put the patient at inacceptable risk.

3.4 Statistical analysis

1. *Sample Size*

We planned to collect a minimum of 10 physicians' answers for each clinical vignette. As a result, we would need a minimal about 5280 physicians' answers (i.e. 528 physicians).

2. *Participants' characteristics*

Participants' descriptive data will be presented with numbers and proportions for categorical variables, and with medians and IQRs for continuous variables.

3. *Threshold for acceptable non-adherence*

For each situation (a given medication in a therapeutic indication), we will report the number (%) of participants choosing each possible response.

For drug omissions, frequencies of dose skipping range from « once a month » to «always acceptable regardless frequency ». Durations of drug holidays range from « two or three days » to « always acceptable regardless duration ».

For each situation, we will use boxplots to represent the participants' answers. We will define the threshold for acceptable non-adherence as the 75^{th} percentile of the distribution of participants' answers for question. We will present the boxplots ordered by two different ways: 1) the 75^{th} percentile of the distribution of participants' answers, and 2) the size of the interquartile range, respectively focusing on two different issues: 1) the threshold for acceptable non-adherence, and 2) the extent to which a consensus among participants was reached.

We will perform sensitivity analyses to assess how the change in the threshold definition may change the results.

4. *Aggregating drug/indications situations*

We will report the results on three different aggregate levels: 1) we will pool drugs from the same class in the same therapeutic indication (for example "statins for secondary cardiovascular prevention" or "calcic inhibitors for high blood pressure"); 2) we will pool drugs from the same class (for example "proton pump inhibitors") and 3) we will pool drugs in the same therapeutic indication (for example "asthma").

We will use complete case analysis to manage missing data. All statistical analyses will involve the use of R V.2.13.1 (http://www.r-project.org).

4. References

1. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353(5):487-97.
2. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. Bmj. 2008;336(7653):1114-7.
3. Ho PM, Magid DJ, Masoudi FA, McClure DL, Rumsfeld JS. Adherence to cardioprotective medications and mortality among patients with diabetes and ischemic heart disease. BMC Cardiovasc Disord. 2006;6:48.
4. Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med. 2000;133(1):21-30.
5. Osterberg LG, Urquhart J, Blaschke TF. Understanding forgiveness: minding and mining the gaps between pharmacokinetics and therapeutics. Clin Pharmacol Ther. 2010;88(4):457-9.
6. Sidorkiewicz S, Tran VT, Cousyn C, Perrodeau E, Ravaud P. Development and validation of an instrument to assess treatment adherence for each individual drug taken by a patient. BMJ Open. 2016;6(5):e010510.
7. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol. 2012;73(5):691-705.
8. Dunbar-Jacob J, Mortimer-Stephens MK. Treatment adherence in chronic disease. J Clin Epidemiol. 2001;54 Suppl 1:S57-60.
9. Ho PM, Rumsfeld JS, Masoudi FA, McClure DL, Plomondon ME, Steiner JF, et al. Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. Arch Intern Med. 2006;166(17):1836-41.
10. Urquhart J, Vrijens B. Commentary on "A Framework for Quantifying the Influence of Adherence and Dose Individualization". Clin Pharmacol Ther. 2016;99(4):354-6.
11. Yao X, Abraham NS, Alexander GC, Crown W, Montori VM, Sangaralingham LR, et al. Effect of Adherence to Oral Anticoagulants on Risk of Stroke and Major Bleeding Among Patients With Atrial Fibrillation. J Am Heart Assoc. 2016;5(2).
12. Prihodova L, Nagyova I, Rosenberger J, Majernikova M, Roland R, Groothoff JW, et al. Adherence in patients in the first year after kidney transplantation and its impact on graft loss and mortality: a cross-sectional and prospective study. J Adv Nurs. 2014;70(12):2871-83.
13. Karve S, Cleves MA, Helm M, Hudson TJ, West DS, Martin BC. Good and poor adherence: optimal cut-point for adherence measures using administrative claims data. Curr Med Res Opin. 2009;25(9):2303-10.
14. Lo-Ciganic WH, Donohue JM, Thorpe JM, Perera S, Thorpe CT, Marcum ZA, et al. Using machine learning to examine medication adherence thresholds and risk of hospitalization. Med Care. 2015;53(8):720-8.

15. Simpson SH, Eurich DT, Majumdar SR, Padwal RS, Tsuyuki RT, Varney J, et al. A meta-analysis of the association between adherence to drug therapy and mortality. BMJ. 2006;333(7557):15.
16. Johnson BF, Whelton A. A Study Design for Comparing the Effects of Missing Daily Doses of Antihypertensive Drugs. Am J Ther. 1994;1(4):260-7.
17. Assawasuwannakit P, Braund R, Duffull SB. Quantification of the Forgiveness of Drugs to Imperfect Adherence. CPT Pharmacometrics Syst Pharmacol. 2015;4(3):e00004.
18. Tran VT, Montori VM, Eton DT, Baruch D, Falissard B, Ravaud P. Development and description of measurement properties of an instrument to assess treatment burden among patients with multiple chronic conditions. BMC Med. 2012;10:68.
19. Urquhart J. How much compliance is enough? Pharm Res. 1996;13(1):10-1.
20. Denhaerynck K, Burkhalter F, Schäfer-Keller P, Steiger J, Bock A, De Geest S. Clinical consequences of non adherence to immunosuppressive medication in kidney transplant patients. Transpl Int. 2009;22(4):441-6.
21. Emsley R. Non-adherence and its consequences: understanding the nature of relapse. World Psychiatry. 2013;12(3):234-5.
22. Grassi G, Seravalle G, Mancia G. Cardiovascular consequences of poor compliance to antihypertensive therapy. Blood Press. 2011;20(4):196-203.
23. Hsu KL, Fink JC, Ginsberg JS, Yoffe M, Zhan M, Fink W, et al. Self-reported Medication Adherence and Adverse Patient Safety Events in CKD. Am J Kidney Dis. 2015;66(4):621-9.
24. Barrett B, Ricco J, Wallace M, Kiefer D, Rakel D. Communicating statin evidence to support shared decision-making. BMC Fam Pract. 2016;17:41.
25. Ancker JS, Senathirajah Y, Kukafka R, Starren JB. Design features of graphs in health risk communication: a systematic review. J Am Med Inform Assoc. 2006;13(6):608-18.
26. Opel DJ, Taylor JA, Phillipi CA, Diekema DS. The intersection of evidence and values in clinical guidelines: who decides what constitutes acceptable risk in the care of children? Hosp Pediatr. 2013;3(2):87-91.
27. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010;138(5):1093-100.
28. Nelson HD, Zakher B, Cantor A, Fu R, Griffin J, O'Meara ES, et al. Risk factors for breast cancer for women aged 40 to 49 years: a systematic review and meta-analysis. Ann Intern Med. 2012;156(9):635-48.
29. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(25 Pt B):2889-934.
30. Guyatt GH, Bombardier C, Tugwell PX. Measuring disease-specific quality of life in clinical trials. CMAJ. 1986;134(8):889-95.
31. Sauermann H, Franzoni C. Crowd science user contribution patterns and their implications. Proc Natl Acad Sci U S A. 2015;112(3):679-84.

5. APPENDIX

1. Questions for medications taken once daily

Le patient vous apprend qu'il saute une prise de ce médicament de temps en temps.
Selon vous, quand le risque encouru pour sa santé devient-il inacceptable?

Pour un saut d'une prise survenant :

- 1 jour par mois
- 2 jours par mois
- 3 jours par mois
- 1 jour par semaine
- 2 jours par semaine
- 3 jours par semaine
- Risque toujours acceptable quelque soit la fréquence des sauts
- Autre :
- Je ne sais pas

Le patient vous apprend qu'il fait des pauses de PLUSIEURS JOURS CONSECUTIFS sans prendre le médicament.
Selon vous, quand le risque encouru pour sa santé devient-il inacceptable?

Pour une pause d'une durée de :

- 2-3 jours
- 4-5 jours
- 6-7 jours
- 2 semaines
- 1 mois
- Risque toujours acceptable quelque soit la durée de la pause
- Autre :
- Je ne sais pas

2. Questions for medications taken twice or three times a day

Le patient vous apprend qu'il saute une prise de ce médicament de temps en temps.
Selon vous, quand le risque encouru pour sa santé devient-il inacceptable?

Pour un saut de prise concernant :

- une prise de la journée, 1 à 2 fois par mois
- toutes les prises, 1 jour par mois
- toutes les prises, 2 jours par mois
- toutes les prises, 3 jours par mois
- toutes les prises, 1 jour par semaine
- toutes les prises, 2 jours par semaine
- toutes les prises, 3 jours par semaine
- Risque toujours acceptable quelque soit la fréquence des sauts
- Autre :
- Je ne sais pas

Le patient vous apprend qu'il fait des pauses de PLUSIEURS JOURS CONSECUTIFS sans prendre le médicament.
Selon vous, quand le risque encouru pour sa santé devient-il inacceptable?

Pour une pause d'une durée de :

- 2-3 jours
- 4-5 jours
- 6-7 jours
- 2 semaines
- 1 mois
- Risque toujours acceptable quelque soit la durée de la pause
- Autre :
- Je ne sais pas