Therapie (2017) xxx, xxx—xxx

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

ROUND TABLE ABOUT FALSE-POSITIVE RESULTS

False-positive results in pharmacoepidemiology and pharmacovigilance

Les faux positifs en pharmaco-épidémiologie et en pharmacovigilance

Julien Bezin[a,b,c], **Pauline Bosco-Levy**[a,c,d], **Antoine Pariente**[a,b,d,*]

[a] *Inserm, UMR 1219, Univ. Bordeaux, Bordeaux population health research center, pharmacoepidemiology team, 33000 Bordeaux, France*
[b] *Direction de la recherche et de l'innovation, CHU de Bordeaux, 33000 Bordeaux, France*
[c] *CIC Bordeaux CIC1401, 33000 Bordeaux, France*
[d] *Service de pharmacologie médicale, CHU de Bordeaux, 33000 Bordeaux, France*

Received 14 September 2016; accepted 19 September 2016

KEYWORDS
False-positive;
Biases;
Pharmacoepidemiology;
Pharmacovigilance;
Drug safety

Summary False-positive constitute an important issue in scientific research. In the domain of drug evaluation, it affects all phases of drug development and assessment, from the very early preclinical studies to the late post-marketing evaluations. The core concern associated with this false-positive is the lack of replicability of the results. Aside from fraud or misconducts, false-positive is often envisioned from the statistical angle, which considers them as a price to pay for type I error in statistical testing, and its inflation in the context of multiple testing. If envisioning this problematic in the context of pharmacoepidemiology and pharmacovigilance however, that both evaluate drugs in an observational settings, information brought by statistical testing and the significance of such should only be considered as additional to the estimates provided and their confidence interval, in a context where differences have to be a clinically meaningful upon everything, and the results appear robust to the biases likely to have affected the studies. In the following article, we consequently illustrate these biases and their consequences in generating false-positive results, through studies and associations between drug use and health outcomes that have been widely disputed.

* Corresponding author. Service de pharmacologie médicale, hôpital Pellegrin, CHU de Bordeaux, 33076 Bordeaux, France.
E-mail address: antoine.pariente@u-bordeaux.fr (A. Pariente).

http://dx.doi.org/10.1016/j.therap.2016.09.020
0040-5957/

Please cite this article in press as: Bezin J, et al. False-positive results in pharmacoepidemiology and pharmacovigilance. Therapie (2017), http://dx.doi.org/10.1016/j.therap.2016.09.020

MOTS CLÉS
Faux positifs ;
Biais ;
Pharmacoépidémiologie ;
Pharmacovigilance ;
Sécurité du médicament

Résumé Les faux positifs constituent une question importante dans la recherche scientifique. Dans le domaine de l'évaluation des médicaments, elle affecte toutes les phases du développement et de l'évaluation des médicaments, depuis les études précliniques très précoces jusqu'à l'évaluation postcommercialisation. La principale préoccupation associée à ce faux positif est le manque de reproductibilité des résultats. Outre la fraude ou les inconduites, le faux positif est souvent envisagé sous un angle statistique, ce qui est considéré comme un prix à payer pour l'erreur de type I dans les tests statistiques, et son inflation dans le contexte de tests multiples. Dans le contexte de la pharmaco-épidémiologie et de la pharmacovigilance, qui évaluent toutes deux les médicaments dans un contexte d'observation, l'information apportée par les tests statistiques et l'importance de ceux-ci ne devraient être considérés comme complémentaires qu'aux estimations fournies et à leur intervalle de confiance. Plus qu'une question de faux-positifs statistiques, la problématique est alors bien davantage d'identifier des différences cliniquement significatives, mises en évidence dans des études aux résultats robustes aux biais. Dans l'article qui suit, nous illustrons ces biais et leurs conséquences dans la production de résultats faux positifs, à travers des études et des associations entre l'usage de drogues et les résultats de santé qui ont été largement contestés.

Abbreviations

ASA	American Statistic Association
EHDs	electronic healthcare databases
ENCePP	European Network of Centres for Pharmacoepidemiology
RCTs	randomized controlled trials (RCTs)

Introduction

Recently, an important thinking was conducted and published by the American Statistic Association (ASA) on the use and places of *P*-values. This reflection led to the publishing of a statement by the ASA on what to do, what to expect and what to pay attention to when performing statistical tests and making use of *P*-values. Manuscripts from some of the main leaders in medical statistics were associated to this published statement, most of which insisted on the issue of false-positive results related to statistical tests. This provided an interesting opportunity to remind the meaning (whatever the significance) of the statistical tests routinely performed in observational studies focusing on drug assessment as well as the origin and the consequences of false-positive results in this pharmacoepidemiology and pharmacovigilance research.

Principles behind the tests

Lots will be said in the manuscripts on false-positive in preclinical studies and on false-positive in clinical studies that are associated with the present paper. I just wish to remind that false-positive implies that a result associated to a statistical test is considered positive, that to help distinguishing between tests that could be considered positive and others, Neyman and Pearson proposed to use a threshold of significance that is based on the *P*-value, and that this *P*-value represents the estimation that the observation is made under the null hypothesis. Indeed, the basis of the statistical test is this null hypothesis, which usually states that there is no difference between groups. If this appears perfectly admissible in a randomized context, it seems much more questionable in an observational setting. Indeed, the proper conditions of the use of the *P*-value and of the Neyman and Pearson threshold for significance is the setting of studies in which ''design and analyses provide effect estimate, confidence interval, and *P*-values estimates that are free of bias''. In an observational setting, it is always an optimistic hypothesis. Actually, we should acknowledge that the use of statistical testing and *P*-values in an observational setting must be thought in order to bring additional information to the observation itself, but should clearly not be considered of primary importance when faced to other types of information (effect size, variations of the estimates through sensitivity analyses, dose/duration response analyses, etc.). That being said, it appears clearly that:

- the use of statistical tests should be restricted to situation where the information it brings will be the most useful (certainly not for the comparison of population characteristics in an observational setting for instance);
- most of the issue concerning false-positive in observational assessment of drugs relates to bias;
- biases concerning the assessment of drugs in an observational setting should be specifically scrutinized when seeking for potentially causal association. The issue concerning false-positive results in this non-randomized setting should be assessed through this angle, and not that of the pure statistical threshold.

False-positive in pharmacoepidemiology

The issue of false-positive in pharmacoepidemiology is made more accurate by the growing use of large electronic healthcare databases (EHDs) for the assessment of drug use-health outcome associations. These EHDs provide, in numerous

Please cite this article in press as: Bezin J, et al. False-positive results in pharmacoepidemiology and pharmacovigilance. Therapie (2017), http://dx.doi.org/10.1016/j.therap.2016.09.020