PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2005; **14**: 365–366
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/pds.1094

EDITORIAL

Causal or casual?

In this issue of the *Journal*, Mines *et al*.[1] report that in the setting studied, patients to whom the antidepressant venlafaxine was prescribed had a higher prevalence of characteristics associated with suicidal risk than patients prescribed fluoxetine or citalopram. The well-conducted research of these authors, all employees of the manufacturer and marketer of venlafaxine (Wyeth Pharmaceuticals), was triggered by three quite recent observational studies that reported a higher rate of fatal overdose with venlafaxine than with SSRI use and subsequent regulatory action restricting venlafaxine prescribing to specialists. The conclusion of the authors is that the results of these observational studies may have been biased due to differences in baseline risk for suicide. Although beyond the intent of this editorial comment, please note the subtle but potentially clinically relevant difference between suicide (attempt) and fatal overdose. In case of a similar risk of suicide for several individual antidepressant drugs, the fatality risk may still differ due to different safety margins when taken in overdose. In this respect, the authors seem to over-interpret their findings in the 'key points'.

More relevant, the article by Mines *et al*. revives an already many years ago posed but still valid question in pharmacoepidemiology, namely 'did the drug bring the problem to the patient, or did the patient bring the problem to the drug'.[2] A very basic validity principle in any etiologic study is that baseline differences with respect to the risk for the outcome under study should be accounted for either in the design or in the analysis. Usually when comparing several representatives of a therapeutic class, the baseline risks for outcomes well-known to be associated with either the course of the disease or its treatment are rarely the same.[3] Normal human behaviour of physicians (new drugs are more frequently used for patients not responding satisfactorily to previous treatment), treatment guidelines, marketing strategy, economic factors and many other poorly understood factors may lead to selective prescribing, especially of new drugs, to relatively polluted populations.[4] Pharmacoepidemiologic research has provided many examples of this channelling phenomenon during the past 15 years.

So, with no doubt about the potential relevance of this phenomenon for patient care, drug evaluation and product life cycle, the question is how to bring this important issue in pharmacoepidemiology and risk management one step further. The usual way to account for imbalance in prognostic factors in etiologic studies is to adjust for these differences in the analysis by multivariable techniques such as logistic regression. Relatively newer techniques such as modelling propensity scores have shown to be a valuable alternative with prospects.[5] Given the study question at issue—does the drug venlafaxine lead to a higher rate of (fatal) suicide (i.e., causal), or is this association (in part) induced by baseline differences between patients (i.e., casual)—it would have been worthwhile not only to demonstrate that such differences do exist, but also to evaluate the influence of these differences on the risk estimates. The observational studies on antidepressants and fatal toxicity (references 2–4 in the Mines article) failed to identify potential differences in prognostic patients characteristics, let alone adjust for it. The article by Mines *et al*., on the other hand, validly looked at these differences in baseline risk, but did not study the clinical outcome of interest. When such a relevant question for patient care is at stake, pharmacoepidemiology should put maximal effort to integrate drug utilisation dynamics into drug exposure-outcome studies and vice versa, in order to contribute relevant and valid knowledge that is, medicine-based evidence.[6] Otherwise the question 'causal or casual' remains unanswered.

* Correspondence to: Dr Toine C. G. Egberts, Professor of clinical pharmacoepidemiology, Utrecht Institute for Pharmaceutical Sciences, PO Box 90107, 3508 Utrecht, The Netherlands.
E-mail: a.c.g.egberts@pharm.uu.nl

Toine C. G. Egberts
Utrecht Institute for Pharmaceutical Sciences,
Utrecht, The Netherlands

Received 15 February 2005
Accepted 16 February 2005

Copyright © 2005 John Wiley & Sons, Ltd.

REFERENCES

1. Mines D, Hill D, Yu H, Novelli L. Prevalence of risk factors for suicide in patients prescribed venlafaxine, fluoxetine and citalopram. *Pharmacoepidemiol Drug Safe* 2005; **14**: 367–372.
2. Petri H, Urquhart J. Channeling bias in the interpretation of drug effects. *Stat Med* 1991; **10**: 577–581.
3. Miettinen OS. The need for randomization in the study of intended effects. *Stat Med* 1983; **2**: 267–271
4. Egberts ACG, Lenderink AW, Koning GHP de, Leufkens HGM. Channeling of three newly introduced antidepressants to patients not responding satisfactorily to previous treatment. *J Clin Psychopharmacol* 1997; **17**: 149–155.
5. Rubin DB. On principles for modeling propensity scores in medical research. *Pharmacoepidemiol Drug Safe* 2004; **13**: 855–857.
6. Heerdink ER, Stolker JJ, Meijer WEE, Hugenholtz GWK, Egberts ACG. Need for medicine-based evidence in pharmacotherapy. *Br J Psych* 2004; **184**: 452.

Copyright © 2005 John Wiley & Sons, Ltd.