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Temporal Patterns of NSAID Spontaneous Adverse Event Reports

The Weber Effect Revisited

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Abstract

Objectives: Determine whether recent US adverse event reports for several nonsteroidal anti-inflammatory drugs (NSAIDs) conform to the temporal pattern observed by Dr JCP Weber in the UK in the early 1980s, i.e. a rising count in the first few years after launch presumably reflecting increased exposure, followed by a decline, presumably reflecting decreased enthusiasm for reporting as adverse events become well known.

Study Setting: US adverse event report data available from the US Food and Drug Administration, reformatted by a commercial vendor.

Methods: For the 5 NSAIDs launched in the US between 1987 and 1993 that had data suitable for this study, we tabulated by year from launch the number of reports and the reporting rate (number of reports per 1000 prescriptions).

Results: The number of reports for 3 of the 5 NSAIDs showed a temporal pattern approximating that described by Weber. The number of reports for the other 2 NSAIDs showed temporal patterns markedly different from that described by Weber. For 4 of the 5 NSAIDs, reporting rates did not decline consistently with time from launch.

Discussion: The temporal patterns of adverse event reports are more complex than those described in Weber's classic report. The number of reports does not reliably rise and then fall after launch and the reporting rate does not reliably decrease with time from launch.

In 1984, Dr JCP Weber of the Department of Health and Social Security of London, UK, published a study describing the reported adverse events of 9 nonsteroidal anti-inflammatory drugs (NSAIDs) then used in the UK.[1] He observed that the number of adverse events typically increased to a peak near the end of the second year of marketing and subsequently declined. This was consistent with the combined results of 2 temporal changes: an initial rise in reports due to increasing patient exposure as the new drug gained market share, followed by a later fall in reports as the reporting-fraction of adverse events declined when practitioners became familiar with the medication and lost interest in reporting such events.

Although Weber clearly recognised that this temporal pattern of adverse event reporting reflected an artifact, at least in the second, downward portion of the curve, the 'Weber Effect' is often invoked in discussing adverse event reports in times and places far removed from the context in which he noted it. To see whether this generalisation is

Table I. The 5 nonsteroidal anti-inflammatory drugs evaluated in the study

Generic name (tradename)	Manufacturer	Date of launch
Diclofenac ('Voltaren')	Geigy	August 1988
Etodolac ('Lodine')	Wyeth Ayerst	April 1991
Flurbiprofen ('Ansaid')	Upjohn	December 1988
Nabumetone ('Relafen')	SmithKline Beecham	February 1992
Oxaprozin ('Daypro')	Searle	January 1993

appropriate, even for the class of medications he originally studied, we sought to replicate Weber's finding for recent US adverse event reports associated with NSAIDs.

Methods

The present study describes the time course of prescriptions and adverse event reports for the 5 NSAIDs that were launched in the US between 1987 and 1993, were still marketed in 1999, and had sufficient exposure for their prescriptions to be estimated in the annual International Medical Statistics reports from launch through to 1999 (table I).[2]

These 5 NSAIDs are indicated for the short and long term treatment of the signs and symptoms of rheumatoid arthritis and osteoarthritis. Diclofenac and flurbiprofen are also indicated for the treatment of ankylosing spondylitis and primary dysmenorrhoea. Flurbiprofen is also indicated for the treatment of acute gout. The US labels for these NSAIDs indicate the following differences regarding their indications and their associations with gastrointestinal bleeding. The available formulations of diclofenac include an enteric-coated tablet that is associated with decreased frequency of gastrointestinal bleeding. Nabumetone is a pro-drug, which may also be associated with a decreased risk of gastrointestinal bleeding. Some degree of cyclo-oxygenase 2 selectivity has been claimed for etodolac and for nabumetone.

Data for this study were taken from the US Food and Drug Administration (FDA)'s database of US adverse event reports as formatted by a commercial vendor.[3] Only spontaneous postmarketing reports were included. Reports were dated according to FDA accession date, the only date available for all reports. A report was classified as serious if it involved a congenital anomaly, death, disability, initiation or prolongation of hospitalisation, or a threat to life. All other reports were classified as nonserious. All reports for the same chemical entity were combined.

It is possible that updates of original reports may be included in the FDA database as new reports, which would lead to over counting. To estimate the magnitude of this issue, we examined reports for which a manufacturer's control number (MCN) was available (over 90% of reports). The number of redundant cases (reports with identical MCNs) was then expressed as a percentage of the total number of reports. If 2 MCNs matched, 1 report was counted as redundant. If 3 matched, 2 were counted as redundant, etc. The relatively low frequency of redundant reports overall, less than 4% for each study agent, permitted the study to proceed without deleting these redundant reports. A further breakdown of these data indicated that redundancy

Table II. Redundant reports as a percentage of total number of reports by medication and seriousness of the report

Drug	Serious reports (%)	Nonserious reports (%)	Overall reports (%)
Diclofenac	7.2	1.9	3.3
Etodolac	6.6	2.3	2.3
Flurbiprofen	2.6	0.8	0.5
Nabumetone	1.5	2.9	2.7
Oxaprozin	6.1	1.6	3.5

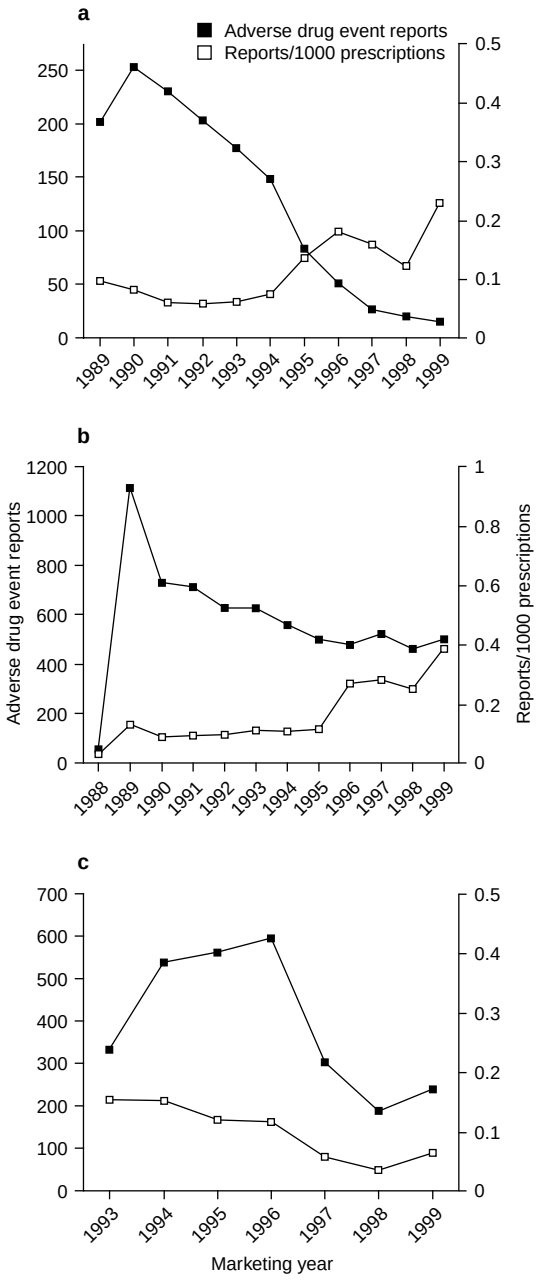

Fig. 1. Adverse drug event reports for (**a**) flurbiprofen, (**b**) diclofenac, and (**c**) oxaprozin (total number of reports and reports per 1000 prescriptions by year).

was more common for serious reports than nonserious reports (table II).

Results

Figure 1a, b and c presents the NSAIDs (flurbiprofen, diclofenac and oxaprozin) whose annual numbers of adverse event reports showed a pattern approximating the one described by Weber. Their annual adverse drug event reports rose during the early years of marketing and subsequently declined. Flurbiprofen and diclofenac showed a single peak of reports 1 to 2 years after marketing began, followed by a decline for each of the later years. Oxaprozin took 4 years to reach its peak. Diclofenac and oxaprozin showed small increases in the number of adverse event reports in the most recent year. Although the adverse event report counts for these 3 drugs behaved in approximately the way described by Weber, the number of reports per 1000 prescriptions for diclofenac and flurbiprofen did not decline with time, but rose over the most recent several years.

Figure 2a and b describes etodolac and nabumetone, respectively. Each of these drugs showed a 2-peaked distribution of reports with a trough in the fourth marketing year. Neither showed a steady decline in adverse event reports per 1000 prescriptions.

Because consumer reports may differ between the US and the UK, we split the adverse event reports according to source (consumer or health professional). This did not change the findings substantially.

Discussion

Weber observed that adverse event reports increase during the first few years after a drug's launch then decrease.[1] Presumably, the initial increase was due to increased sales and exposure and the subsequent decrease was due to decreased reports per exposure and per event. The present study found temporal patterns of adverse event reporting that differed substantially from those described by Weber. This is not entirely surprising. Though both reports focused on NSAIDs, the present study is

based on data from a different time and place and reflects different reporting practices from those that were in place in the UK during the late 1970s and early 1980s.[4] Most notably the US currently collects reports of adverse events, rather than only reports of adverse reactions, and collects reports from all sources rather than reports from physicians only.

In our study, each of the medications that showed a second peak in the number of reports was the subject of publicity shortly before the second peak and that publicity may have affected reporting.[5-7] Whatever the mechanism behind these peaks, however, the present report makes it quite clear that for current US postmarketing adverse event reporting, one cannot assume that the number of reports will rise during the first few years and subsequently decline in the classic pattern that Weber described so clearly. Therefore, reference to the 'Weber Effect' as the explanation for all temporal patterns of adverse event reports in widely different circumstances of time and place is not appropriate.

In the course of developing the data for the present report, we needed to address the possibility of redundant reports, i.e. of several versions of the same report being tallied as if they were separate reports. Using manufacturers' control numbers to identify such redundant reports, we were able to demonstrate that they represent only a small proportion of all reports and thus, could not account for our findings. However, we also observed that the proportion of redundant reports is substantially higher among serious adverse event reports than among nonserious reports. This raises the possibility that redundant reports would be sufficiently common to cause serious difficulties in studies that focus on drugs used to treat very complicated or severe diseases, or in studies that focus on particularly severe adverse events, e.g. deaths.

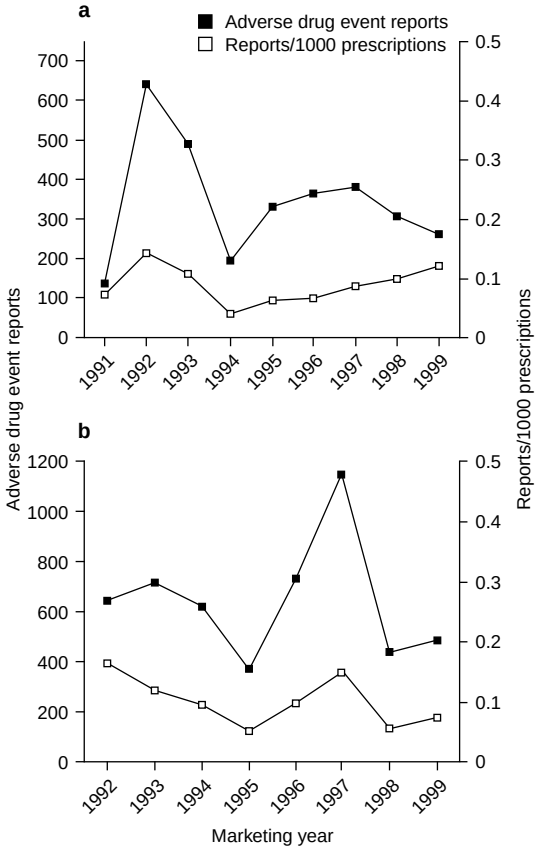

Fig. 2. Adverse drug event reports for (**a**) etodolac, and (**b**) nabumetone (total number of reports and reports per 1000 prescriptions by year).

Conclusions

The Weber Effect is a widely invoked observation that the number of spontaneous adverse events for a medication tends to increase over its first few years after launch, and subsequently decrease. However, even among NSAIDs, the medications on which this observation was based, other temporal distributions, e.g. 2-peaked distributions, are observed, and reporting rates (reports/1000 prescriptions) may increase rather than decrease with time. Further research in adverse event reporting trends could usefully examine the issue of redundant reports, whose prevalence appears to be higher among serious than among nonserious adverse events.

Acknowledgements

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