PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Oral assumption of benzididamine-containing vaginal preparations in association with tv advertising in Italy: analysis of cases handled by a national poison control centre
AUTHORS	Laura Settimi, Franca Davanzo, Lauria L, Maria Luisa Casini, Fernanda Ferrazi

VERSION 1 - REVIEW

REVIEWER	Salomé Ballesteros. Servicio de Información Toxicológica. Instituto Nacional de Toxciología y Ciencias Forenses, Madrid, Spain
REVIEW RETURNED	29/06/2011

THE STUDY	It would be neccesary to define what is "case of interest", and add inclusion and exclusion criteria. Dates should be standarised References in pag 5 are incorrectly ordered. Gramatic errors and definition confusion: - Benzydamine is incorrectly written in several pages -"Assumption" instead of "ingestion" - Pg 4, line 32; "The aim..." - Pg 5 line 15: "according to... -Pg 6 line 5: period, and 67... - Pg 5, line 28: Focusing the attention...: incorrect meaning -Pg5, lines 44...: outcome can be fatal, degrees of severity are mild, moderate and severe (not high...) - Pg 5 lines 52: heartburn is Pyrosis. Pharyngeal (not pharingeal) - Pg 7 lines 8, 14...: Sold out is not the right word - Please check pg 8 lines 3 Arrieta. line 4: Preparations Pag 12, table 2: heartburn is pyrosis. Including cases who... should be with two * (**)
RESULTS & CONCLUSIONS	No references and discuison with them are included in the "Comments" section. Limitations of the study such as the increasing number of exposure could be due to over-reporting, more than actually more intoxications, should be added

REVIEWER	Elaine Donohoe Specialist in Poisons Information NPIC Dublin Ireland
REVIEW RETURNED	04/07/2011

THE STUDY	While the data set is correct and appropriate for this study, I am not sufficiently competant in statistical methods to determine whether the correct tests have been used (specifically the analysis of "means"). I would suggest that a statistician be consulted to ensure

	the findings are accurate.
REVIEWER	Barbara Mintzes Assistant Professor Department of Anesthesiology, Pharmacology & Therapeutics University of British Columbia Canada I have no competing interests.
REVIEW RETURNED	30/07/2011

THE STUDY	Settimi and colleagues have examined the rate of reporting of adverse events to a national poison control centre in Milan for benzydamine-containing preparations pre- and post- a shift in status from pharmacy-supervised to over-the-counter. The latter allows advertising of the public on television; the former does not. Following the shift in status, an intensive advertising campaign was launched. The poison control centre observed an increase in the rate of accidental poisoning due to oral ingestion of a product intended for vaginal use, and the Italian Ministry of Health required the advertisement to be revised. The current article is a retrospective analysis of reports to the poison control centre during three time periods: pre-advertising (5 years), during the advertising campaign (3 months) and post the campaign (10 months). The authors express the reporting rates during these 3 periods as mean # of cases per day, and compare observed versus expected rates during the advertising and post-advertising periods, with expected rates based on the pre-advertising period. Strengths: This is a very interesting exploration of the public health impact of an advertising campaign. As the authors note, the direct health impacts of advertising of health products have been subject to very little scrutiny. Health impacts are often expected from increased use and from specific cases of misleading or inaccurate messages. In this case the message on mode of use appears to have been misleading. The advertising campaign was time-limited, allowing clear demarcation between the period pre- and post advertising, another study strength. The strongest side of the argument made by the authors relates to the shift in proportion of types of reactions reported pre- and post-advertising campaign, and the large increase in reactions in the population group targeted by advertising. This could be developed further, with less text spent on the overall rates (I explain below why I am suggesting this). Some concerns about the analysis that should be addressed: 1) Reporting rates - The calculation of expected # of cases per day per time period assumes that the denominator, the # of people exposed, has not changed. The authors were unable to obtain full data on sales from the manufacturer. However, the information that they obtained for December 2009 versus November 2009 is interpreted as being consistent with an over 5-fold increase in the # of packs sold per day after the ad campaign, compared with beforehand. It is possible that sales continued to rise. The potential increase in the denominator, the # exposed, needs fuller discussion. - If the authors' main point is that an increased rate of harm has occurred over time, and that the rate of harm per # exposed is irrelevant, this should be clearly stated. Advertising might have led to harm through increased overall use, higher exposure levels, especially if the likelihood of benefit is

	minimal in general, or if increased use is among those with milder symptoms, less likely to benefit. Some discussion of the product's effectiveness and place in therapy would be helpful, especially if it has been evaluated in comparison with other symptomatic treatments. Also it would be useful to know what exactly its indication for use is. If it is for unspecified vaginal itching, is there a problem with use instead of testing and effective treatment of infections, and especially of sexually transmitted diseases? (I do not know the product so am simply asking for clarification in the text.) - The authors' numerator is not necessarily complete, if it is based on spontaneous adverse event reporting. Adverse drug reactions are notoriously under-reported (estimated at <10%, but empirical research indicating much lower than 10%); if the situation in Milan, for this product, or for these types of events differs, this should be noted. Also it's not clear whether the poison control centre receives all adverse drug reaction reports, or if there is also another reporting system. Or are only specific types of events (overdoses, poisonings? Reported to the centre). In terms of the numerator, it would also be useful to know what area of Italy is covered by the centre in Milan. The authors have noted that 60% of reports of poisoning are covered, but not whether this is based on geographic coverage or on the types of reports made. 2) Two changes occurred around the same time period: - a shift from pharmacy-supervised status to over-the-counter status - the television advertising campaign Could any of the increases in poisoning have occurred because of the switch to OTC status, which would have eliminated the requirement for provision by a pharmacist, who might have provided counselling and instructions? Do any of the data collected suggest this or suggest that this is not the case? It would be worth discussing the difference between the 'advertising' and 'post-advertising' period within this context as the latter period is 3) Additional clarifications needed: - if there were 216 cases exposed to BHC-containing vaginal preparations, why were any of these cases in men? Are these all cases of accidental poisoning? Table 2 does not mention proportion of men and women in the three periods, although this is discussed in the text; it would be useful to include in the table. - it is not clear why only 88 of the 216 cases were judged to have had BHC-related effects. This product has been on the market a long time but it is possible that not all of its adverse effects are known. Sometimes drugs in long use are removed from the market as a result of newly recognized severe adverse events, usually very infrequent events. If this possibility (unrecognized BHC-related events) has been excluded, an explanatory sentence or two would be helpful. Or is this related to the events listed under 'severity of outcomes' – none in Table 2? Why would asymptomatic cases of poisoning have been reported (additional information on reporting procedures would explain this.) - As noted above, there is a problem with the assumption behind the calculation of 'expected' versus 'observed' in Table 1 because of the likely shift in denominators of numbers exposed. For women, it is possible that even with an assumed 5-fold or 10-fold increase in sales, the rate in the advertising period would have been higher than expected. If sales data are available for a longer observed period, calculations should be based on # exposed, if not, it would be worth carrying out a sensitivity analysis with a range of assumptions on numbers exposed. - Figure 1 is very impressive; I would leave Figure 2 out as not really

	needed. 4) Television advertising campaign It would be helpful to include a description of the television commercial, ideally with an image and/or translated quote from the transcript in a box, but if space does not allow for this, a brief paragraph is needed, describing the main health claims and images used. If the Ministry of Health's letter to the company outlined the problems, a quote could be included. One of the most interesting sides of this paper is that it is an exploration of the effects of an advertising campaign that was judged by Italian regulatory authorities to be illegal because of misleading information presentation. 5) Language and spelling: there are a number of spelling mistakes in the text, and a need for English –language editing. For example the term 'oral assumption' should be avoided; it should be oral ingestion or oral use.

VERSION 1 – AUTHOR RESPONSE

We modified the manuscript "Oral assumption of benzydamine-containing gynaecological preparations in association with TV advertising in Italy: analysis of cases managed by a National poison control centre" (New title: Oral ingestion of a topical benzydidamine hydrochloride-containing gynaecological preparation in association with TV advertising in Italy: Analysis of cases managed by a national poison control centre") according to the referees' comments and suggestions.

Regarding the comments made by Dr. Ballesteros, the manuscript has been modified as follows. With specific reference to the case definition, in the "Materials and methods" we have stated that the study included all cases of suspected or ascertained exposure to a benzydamine-containing gynaecological preparation advertised in Italy and reported to the Poison Control Centre in Milan (PCCM) during the three observation periods. Regarding the possibility of over-reporting, since the cases were drawn from a database containing routinely collected data on human exposure to pharmaceutical and non-pharmaceutical agents and no new procedures for collecting data were introduced during the study period, we can reasonably assume that our data were not affected by over-reporting.

The discussion has been drastically modified, including the addition of references to the very few studies performed. We have also discussed the limitations of the study. We have also corrected all of the typographical errors indicated.

With reference to Dr. Mintzes' suggestions and comments, we managed to acquire more data on sales from the manufacturer and used these data in the analyses. In particular, as reported in the "Materials and methods" section, we used the information provided by month from November 2009 to October 2010 to estimate the relative increase in the quantity of packages sold per day in the advertisement and post-advertisement periods. These values were considered proxies of the relative increase of the population at risk of exposure and used as multiplying factors to calculate the expected number of cases per period. The "Introduction" section has been modified to include indications on the use of the advertised preparation. We have also included a short description of the main message of the advertisement. In the "Materials and methods" more information on the activity carried out by the PCCM has been provided. In the "Results" section, Figure 2 has been eliminated; the contents of Table 1 have been modified in accordance with the results of the new analysis of the adjusted O/E ratio. Table 2 has been extended to include the proportion of female cases by period; a short description of the main characteristics of male patients by period has now been included in the text. In the "Comments" section, we have addressed the issues suggested by Dr. Mintzes.

VERSION 2 – REVIEW

REVIEWER	S. Ballesteros. Médico Facultativo, Servicio Información Toxicológica, Instituto Nacional de Toxicología y Ciencias Forenses, Madrid, Spain
REVIEW RETURNED	22/10/2011

GENERAL COMMENTS	Check minor errros: Title: ingestion (not assumption), benzydamine (not benzydidamine) Introduction: GI: gastrointestinal References: ref 8 Ballesteros (not Ballestros), ref 16, Parlament, products. ref 20: Sweetening

REVIEWER	Barbara Mintzes Assistant Professor Department of Anesthesiology, Pharmacology & Therapeutics University of British Columbia Vancouver, B.C. Canada I have no competing interests to declare.
REVIEW RETURNED	02/11/2011

GENERAL COMMENTS	The article is clear and well-presented and you have done an excellent job of revising the analysis and presentation in response to the previous comments. I have only some very minor suggestions: 1) the term 'assumption' in the title should be replaced with 'ingestion' 2) the acronym DTCA should not be used in the text. This acronym is used to refer to direct-to-consumer advertising of prescription-only medicines, and it will create unnecessary confusion to apply it to advertising of over-the-counter medicines. You can simply say 'advertising to the public' instead; 3) It is wonderful that you were able to get additional data on sales from the manufacturer, as this strengthens the case you are making concerning the additional adverse events. In the section on the sales data and daily sales, it was not 100% clear to me which part of the information was actual sales data and which part was an estimate. For example, I didn't know whether you had data on monthly sales or only summarized sales data over the entire period, or sales data over 2 or more periods that helped you to frame your estimates. You probably only need one extra explanatory sentence stating what data you have. 4) where you report the numbers of cases suffering BHC-related effects, you should add a qualifier 'recognized BHC-related effects'. The others may have been suffering BHC-related effects as well, given that the suffered ill effects after ingesting BHC, but these effects have not been described in the literature. I have no other suggestions. I found the results reporting, the discussion and the tables very clear and well-presented, and the article a pleasures to read.

VERSION 2 – AUTHOR RESPONSE

the authors of the Manuscript ID bmjopen-2011-000204.R1 entitled "ORAL ASSUMPTION OF A TOPICAL BENZYDAMINE-CONTAINING GYNAECOLOGICAL PREPARATION IN ASSOCIATION WITH TELEVISION ADVERTISING IN ITALY: ANALYSIS OF CASES MANAGED BY A NATIONAL POISON CONTROL CENTRE" wish to express their gratitude to the reviewers for their indications and encouragements.

The new version of the manuscript had been emended according to the reviewers last suggestions.