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THERAPIES

HEADING: Clinical pharmacology

Does the capture-recapture method can be used for estimating the incidence of problematic off-label prescriptions?

A capture-recapture method for estimating the incidence of off-label prescription

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Summary

The local/regional incidence of off-label prescriptions can be difficult to estimate. Capture-recapture models can be used to indirectly estimate population sizes. Here, we used a capture-recapture model to estimate the number of patients treated off-label with baclofen for alcohol use disorder in northern France in 2013. Three capture sources were used: (i) the active case file at the region's largest Addiction Unit, (ii) the regional pharmacovigilance centre, and (iii) a sample of community pharmacies. After between-source overlaps had been identified, we used a log-linear model to produced eight estimates. Two models displayed the best goodness-of-fit, with estimates [95% confidence interval] of 1123 [714–2162] and 2180 [1598–2870] subjects, respectively. These two values are in line with a previous estimate of 1,624 patients, based on an analysis of the French national health insurance database in 2013. Capture-recapture methods can be usefully applied to estimate the prevalence of OLPs in a specific geographical area, when direct counting is not feasible or the estimate through claim database is not possible.

Keywords

Capture-recapture method; Off-label; Baclofen; Alcohol use disorder

Abbreviations

ADRs: adverse drug reactions

AUD: alcohol use disorder

CI: confidence interval

NPdC: Nord – Pas-de-Calais (region)

OLP: off-label prescribing

SD: standard deviation

Introduction

Off-label prescribing (OLP) consist of using a drug outside the indication and/or the dose range defined in the marketing authorization. It has been estimated that OLP account for around 20% of all prescriptions by office-based physicians [1]. Moreover, some types of OLP are subject to prescribing trends that spread quickly among patients and prescribers – even when evidence for efficacy and safety is limited or lacking. Hence, it is important to monitor the regional or national incidence of this type of prescribing practice. OLP and the corresponding patient populations may be difficult to correctly screen and tally. The implementation of registries or other prospective data collection systems is costly and time-consuming, and these approaches do not always include the populations of interest [2]. Identifying OLP in claims databases is not easy even if a recent study has demonstrated that monitoring misuse or potential misuse of drug is possible with data from the French health insurance databases [3]. Consequently, indirect methods may be of value for estimating the regional or national incidence of OLP practices.

The capture-recapture method was initially developed for estimating the size of animal populations. This counting procedure is based on capturing, marking and recapturing individuals in the target population [4]. The method was subsequently applied to epidemiology [5] and then pharmacoepidemiology, where it has been used (for example) to assess the frequency of adverse drug reactions (ADRs) within an hospital [6] and to determine the frequency of hospitalizations related to drug use [7]. However, the capture-recapture method has never previously been used to estimate the incidence of an OLP practice.

The French spreading of off-label prescription of baclofen in alcohol use disorder (AUD) has been observed in France since 2008 [8]. Baclofen is a gamma aminobutyric acid type B receptor agonist that was initially authorized in an indication of spasticity at doses of up to 80 mg per day. In France, OLP of baclofen has been linked to the administration of doses of as much as 300 mg per day [8, 9]. This prescribing practice has been regulated in France since 2014, following the publication of a temporary recommendation for use issued by the French Drug Agency [10].

Although the off-label use of baclofen for AUD has been frequently promoted in the media [8], few studies have assessed the extent of this practice. In 2014, two studies reported that OLP of baclofen were common among both general practitioners and addiction specialists [9, 11]. In 2015,

an exhaustive study of the French national health insurance claims database estimated that 50 000 to 100 000 patients had been treated off-label with baclofen between 2007 and 2013 [12].

In the present study, we applied a capture-recapture method to estimate the number of individuals having been treated off-label with baclofen in the Nord – Pas-de-Calais (NPdC) region of northern France in 2013.

Materials and methods

Setting

The present study was conducted in the NPdC region of France, which had an estimated total population of 4,127,229 inhabitants on January 1st, 2014 [13, 14]. Only the individuals treated with baclofen for AUD were eligible for inclusion.

Capture

Three data sources were used to identify eligible patients, whose initials, gender, age, and place of residence were recorded.

The first source (referred to hereafter as list #1) consisted of the active case file at Lille university hospital's addiction unit (the region's largest addiction unit).The case file was screened for one or more baclofen prescriptions in an indication of AUD during 2013.

The second source (list #2) was the regional pharmacovigilance centre (*centre régional de pharmacovigilance*, Lille, France), which collects all reports of ADRs in the NPdC region. This includes all ADRs related to the use of baclofen for AUD in the region [15]. List#2 thus comprised all patients for whom an ADR related to the use of baclofen in AUD was reported in 2013. Many of the ADRs were reported by the Lille addiction unit, via a specific collaboration system in which baclofen-related ADRs were systematically reported [16]. This between-source overlap was taken into account in the modelling process described below.

The third source (list #3) comprised patients who had been given a prescription of baclofen for AUD by a sample of community pharmacies in the NPdC region between July and November 2013. This sample was extracted from a specific ad hoc survey about baclofen dispensing by the

region's community pharmacies [17]. In addition to the prescription data, the pharmacists were also asked to state whether the patients were consulting the prescriber in list #1.

Recapture

After data collection and pre-processing, the three lists were cross-checked in order to discriminate between single and multiple occurrences, and determine the number of overlaps. Non-captured cases were assessed by applying a log-linear regression model for capture–recapture analysis.

Ethical aspects

The study was approved by the ad hoc ethics committee (*Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé*, reference: 15.861), and was registered with the French National Data Protection Commission (*Commission nationale informatique et liberté*: reference DA916019) with regard to data de-identification procedures.

Statistical analysis

Age was expressed as the mean ± standard deviation (SD). Patient gender and addiction were expressed as the number (percentage). We applied the an capture-recapture method and three incomplete data sources to estimate the total number of patients treated off-label with baclofen for AUD in 2013 in the NPdC region. Based on the number of overlaps and non-overlaps between the three-lists, we estimated the number of uncaptured cases through log-linear Poisson regression models [18]. Since one of the possible overlaps was not observed, we added a pseudocount of one in each possible overlap and thus improved the prediction of the number of uncaptured cases, as previously recommended [19]. All possible Poisson regression models were fitted, and we selected the best-fitting model as a compromise between the deviance, the Akaike information criterion, and the Bayesian information criterion [18].

For each model, the 95% confidence interval (CI) for the number of treated patients was estimated using a bootstrap method with 500 samples.

The exhaustiveness of a given source was defined as the ratio between the number of cases identified in the source and the total number of cases estimated in the best-fitting model. All statistical analyses were performed with SAS software (version 9.3, SAS Institute Inc., Cary, NC).

Results

Capture

Lists #1, #2 and #3 respectively contained 76, 138, and 45 patients (Table 1). Most of the patients were male (i.e. 69.7%, 67.4% and 60.0% of the patients in lists #1, #2 and #3, respectively), and the mean age was 51.6, 48.7, and 49.3, respectively. The ages ranged from 22 to 78 (list #1), 22 to 74 (list #2), and 26 to 72 (list #3).

Overlaps

To avoid duplications, multiple occurrences were identified; there were 26 overlaps when comparing lists #1 and #2, 6 overlaps for lists #2 and #3, and 2 overlaps for lists #1 and #3 (Fig. 1). Two patients were found in all three lists. Hence, after cross-checks, the three data sources captured a total of 227 patients.

Capture-recapture

Log-linear regression capture-recapture modelling produced eight estimates. Model #5 showed the best goodness of fit (Table 2) and gave an estimate [95% CI] of 1123 [714–2162] baclofen-treated individuals in the NPdC region in 2013. The second best-fitting model (#3) gave an estimate of 2180 [1598–2870] individuals.

On the basis of model #5, the level of exhaustiveness [95%CI] was determined to be 6.8% [5.3 – 8.3%] for list #1, 12.3% [10.4 – 14.2%] for list #2, and 2.9% [2.9 – 5.1%] for list #3 (Table 3). The combination of the lists #1 and 2 was closest (level of exhaustiveness: 19.1%) to the combination of all three lists (20.3%).

Discussion

The main objective of the present study was to use a capture-recapture method to estimate the incidence of OLP of baclofen for AUD in the NPdC region in 2013. Two of the eight models met our statistical criteria and provided relatively similar estimates [95% CI]: 1123 [714–2162] for model #5, and 2,180 [1598–2870] for model #3. One could argue over which of the two models was better from a statistical standpoint. We choose to assess the external validity of both estimates by comparing them with other available estimated data on the number of patients treated with baclofen in the NPdC region in 2013.

According to an analysis of the French national health insurance database, 26,153 patients started taking baclofen for AUD in 2013 in France [12]. Although regional data were not available in the latter study, scaling for the number of inhabitants in the NPdC region at the time (6.2% of the national population in 2013) gives an estimated value of 1624 patients potentially treated with baclofen in 2013 in the French region of NPdC [13, 14]. This number stands strictly between our two statistically relevant models, providing an external validity. Naturally, this direct, unadjusted comparison should be interpreted with caution because the prevalence of AUD and the OLP of baclofen vary from one region of France to another. Nevertheless, it comfirms the relevance of the estimates from the capture/recapture method.

With regard to the models' internal validity, there are several recommendations for data collection and list building in capture-recapture studies [19]. Firstly, the study population has to be "closed". This condition was met in the present study because we only assessed 2013. Secondly, all identified subjects must meet the same criteria, i.e. actual treatment with baclofen for AUD. This condition was undoubted met for lists #1 and #2 but is subject to debate for list #3, in which community pharmacists were asked to report patients with a prescription for baclofen in AUD. It was not possible to retrospectively confirm that these patients had actually taken the prescribed baclofen for this indication. However, owing to the off-label particularity (high dose prescription of baclofen) and the popularity of baclofen use for AUD in France [8], we consider that the pharmacists were rarely mistaken in this respect. Thirdly, subjects must be unambiguously identified. In the present study, the patients were identified by their initials, age, and place of residence. Although the risk of error during the overlap detection process was low, it is not possible to totally rule out this risk. Fourthly, another important aspect of internal validity is data independence. In cases of non-independence, patients identified in one list may be overrepresented in at least one of the other lists [7]. In fact, lists #1 and #2 had some overlaps. The baclofen

prescriber in list #1 was a member of a regional network for the systematic reporting baclofen-related ADRs [15, 16]. Consequently, the patients in list #1 were very likely to belong to list #2 as well. However, the non-independence between lists #1 and #2 was taken into account by our log-linear modelling, and models #5 and #3 included this overlap in their calculation of the estimate. Lastly, individuals in capture-recapture studies must have a similar likelihood of being captured in each source. This aspect constitutes the main limitation of the present study. List #1 concerned a single baclofen prescriber. Although this prescriber worked in the region's largest university hospital, he could definitely not have issued all the baclofen prescriptions in the region. Indeed, there are approximately 45 addiction units in the region and 15 000 GPs, that could potentially had prescribed baclofen for AUD [20]. Moreover, list #3 was built from a survey of community pharmacies over a 5-month-period in 2013. Patients who started taking baclofen after the study period or stopped taking baclofen before the study period were not included in list #3. Furthermore, only 216 community pharmacies were asked for the survey among 1485 in the region [21].

The age and the sex ratio of patients treated with baclofen for AUD are varying according to the three sources, and, we can suppose, to the type of prescriber. Indeed, the characteristics of the patients may be different if they are seeking an addiction physician at an university hospital or a GP. Most of the data concerning the safety of baclofen in AUD have been performed in patients who were seeking addiction specialists [15, 22-24]. For example, in our study, which include a majority of prescriptions issued by addiction specialist, men represent 65.6% of the patients treated with baclofen for AUD but in a French study, conducted among the French health insurance data base, most of the prescriptions of baclofen for AUD were made by general practitioner (70.7%) and men accounted for 56.2% of the patients treated with baclofen for AUD [25]. Moreover, the same study has highlighted a risk of serious adverse events, like hospitalizations, and an increased risk of death in patients treated with high dose (> 75 mg/j) of baclofen for AUD [25].

There is a need to obtain data from the real-world setting, because most of studies investigating potential benefits and/or harms of baclofen for AUD in France came from specialized centres and selected patients. It becomes especially accurate as the a marketing authorization was granted for baclofen in AUD (maximum dose of 80 mg/d) [26].

Despite limitations, our two main estimates of the number of subjects treated with baclofen for AUD in the NPdC region (1123 and 2180) are consistent with the previous estimate from the French national health insurance claims database. These findings suggest that capture-recapture methods can be usefully applied to estimate the prevalence of OLPs in a specific geographical area, when direct counting is not feasible or the estimate through claim database is not possible.

Authors' contributions

MA and SG drafted the manuscript, contributed to study design and interpretation of results.

BR drafted the manuscript and contributed to the interpretation of results.

HB and JL performed data analysis and contributed to the interpretation of results.

EJ contributed to study design and interpretation of results.

RB contributed to study design.

All authors reviewed and approved the final manuscript

Disclosure of interest

BR was the main investigator of a study on high-dose baclofen funded by Ethypharm, and he received fees for lectures or consultancy from Lundbeck and Ethypharm.

RB has received fees for lectures from Lundbeck.

MA, SG, HB, JL and EJ have no conflict of interest.

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Table 1. Distribution of the individuals receiving OLPs of baclofen by gender, age and prescriber

	List #1* N = 76	List #2* N = 138	List #3* N = 45	All lists[§] N = 227
Males, n (%)	53 (69.7)	93 (67.4)	27 (60.0)	149 (65.6)
Age, years, mean (SD)	51.6 (12.2)	48.7 (10.4)	49.3 (12.4)	49.6 (11.0)
Number of patients consulting an addiction physician, n (%)	76 (100.0)	135 (97.8)	19 (42.2)	198 (78.0)

N: number of occurrences; List #1: prescriptions issued by an addiction physician; List #2: ADR notifications; List #3: pharmacy dispensing records.
* Occurrences captured in each list.
[§] Total occurrences captured (multiple occurrences were counted only once).
OLP: off-label prescribing

Table 2. Number of patients treated with baclofen for AUD in 2013 in the Nord – Pas-de-Calais region of France, as estimated with the different capture-recapture models.

#	Description	Estimated number of patients treated off-label	95% confidence interval		Deviance	Degrees of freedom	Akaike information criterion	Bayesian information criterion
			Lower limit	Upper limit				
1	1 2 3 12 23 13	3600	1172	16418	0	0	-	-
2	1 2 3 12 13	1073	626	2567	1.33	1	44.26	43.94
3	1 2 3 12 23	2180	**1598**	**2870**	0.37	1	43.31	42.98
4	1 2 3 13 23	446	366	601	4.58	1	47.52	47.20
5	1 2 3 12	1123	**714**	**2162**	1.37	2	42.3	42.04
6	1 2 3 13	534	419	706	9.96	2	50.89	50.62
7	1 2 3 23	502	401	675	9.32	2	50.26	49.99
8	1 2 3	580	461	739	12.92	3	51.87	51.65

1, 2 and 3 are the three lists taken alone: list #1, list #2 and list #3. 12, 13 or 23 are the interactions between the corresponding sources.
AUD: alcohol use disorder

Table 3. Exhaustiveness of the data sources, using model 5 estimate

Data source	*n*	E%	[95%CI] for E	
			Lower limit	Upper limit
List #1	76	6.8	5.3	8.3
List #2	138	12.3	10.4	14.2
List #3	45	4.0	2.9	5.1
List #1, List #2	214	19.1	16.8	21.4
List #1, List #3	121	10.8	9.0	12.6
List #2, List #3	183	16.4	14.2	18.6
Lists #1, #2 and #3	227	20.3	17.9	22.7

Data are given for the three lists alone and then for the various combinations.
CI: confidence interval; n: number of treated patients; E: exhaustiveness.

Figure 1. Numbers of patients captured in lists #1, #2 and #3, and the number of overlaps.