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ORIGINAL RESEARCH ARTICLE

Performance of the Standardised MedDRA® Queries for Case Retrieval in the French Spontaneous Reporting Database

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Abstract

Objective The objective of this study was to evaluate the performance of Standardised MedDRA® Queries (SMQs) in adverse drug reaction (ADR) identification.

Methods ADR cases included in the last complete year of the French Pharmacovigilance database for research were used to test four SMQs (narrow and broad): agranulocytosis, demyelination, osteonecrosis and psychosis. Reference cases were identified by free-text search and validated by two authors. Sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) of narrow and broad searches of each SMQ were calculated and reported as proportions with 95 % exact confidence interval (CI).

Results Among 20,830 cases reported in 2009, 337 validated cases of agranulocytosis, 17 of demyelination, 52 of osteonecrosis and 230 of psychosis were included in the reference sets. Estimations of SMQ narrow search performance were as follows: Se 62.9 % (95 % CI 57.5–68.1) and PPV 46.8 % (95 % CI 42.1–51.5) for agranulocytosis; Se 88.2 % (95 % CI 63.6–98.5) and PPV 34.1 % (95 % CI 20.5–49.9) for demyelination; Se 94.2 % (95 % CI 84.1–98.8) and PPV 74.2 % (95 % CI 62.0–84.2) for osteonecrosis; and Se 75.1 % (95 % CI 69.0–80.6) and PPV 87.8 % (95 % CI 82.3–92.0) for psychosis. Results obtained using the broad search were similar except for PPV concerning osteonecrosis (52.7 % [95 % CI 42.1–63.1]) and psychosis (61.4 % [95 % CI 55.7–66.8]). For all selected SMQs, Sp and

Key Points

This is the first study evaluating the performance of Standardised MedDRA® Queries (SMQs) for case retrieval in a national spontaneous reporting database over a 1-year period

Among four SMQs (agranulocytosis, psychosis, demyelination and osteonecrosis), the best performance was obtained using SMQ osteonecrosis, whereas the worst was found with SMQ agranulocytosis. Little or no difference in performance was found between the narrow and broad versions of a given SMQ

Heterogeneous performance among other SMQs (excluding algorithmic ones) could be expected

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NPV were greater than 98 % for both narrow and broad searches.

Conclusion Heterogeneous performance of SMQs for case retrieval was found and seems to be related to the characteristics of the condition of interest. It could therefore be expected that for other SMQs, performance may be affected in the same manner.

1 Introduction

The *Medical Dictionary for Regulatory Activities* (MedDRA®)[1] [managed by Maintenance and Support Services Organization (MMSO[2])] was designed to classify a wide range of indications and adverse events and it is mandatory for reporting adverse drug reactions (ADRs) in some countries [1]. MedDRA® terms are arranged in a five-tiered *multi-axial hierarchy*, and low level terms (LLTs) are currently used for data entry in pharmacovigilance databases, as these can match easily with the actual adverse event (there are approximately 70,000 LLTs). However, its high degree of granularity leads to the use of a more aggregated level of terms [preferred terms (PTs)] in order to identify cases for signal detection activities (e.g. the PT "urticaria" includes about 40 LLTs such as "urticaria localized" or "urticaria, unspecified" [2, 3]. As MedDRA® contains more than 20,000 PTs, this level is also often too granular, leading to a risk of not retrieving all true cases. Thus, a more sensitive level is often needed to retrieve a sufficient number of cases for pharmacovigilance activities and signal detection, but the use of higher level terms [high level term (HLT); high level group term (HLGT); system organ class (SOC)] could include vastly different medical concepts [2]. To address these limitations, and to standardise the case retrieval in a MedDRA®-coded database, a small number of predefined searches or special search categories (SSCs) were created; these were simple groupings of associated PTs referring to the same medical concept, but were limited in scope [4]. This led to the development of standardised MedDRA® queries (SMQs) [5, 6]. SMQs are groupings of PTs that represent signs, symptoms, investigations or diagnoses likely to be relevant to a defined medical condition or area of interest. Most SMQs have two different types of search: the narrow search is composed of terms that are without any reasonable doubt related to a selected event (e.g. the PT "bone marrow failure" is per se an indicator of an agranulocytosis); the broad search includes terms of the narrow one and terms that could be related to an event of interest, but for which there exists a degree of uncertainty (e.g. sepsis could be a symptom of agranulocytosis, but could also be related to other causes). Thus, the narrow search is intended to be more specific, while the broad one is intended to be more sensitive [5]. Certain SMQs are a series of queries related to one another in a hierarchical relationship (hierarchical SMQs); these consist of one or more subordinate SMQs that could be combined to create a superordinate, more inclusive SMQ. In some cases, a given SMQ can be organised with an algorithmic feature to produce the most relevant output [5, 7].

During development SMQs are tested to ensure that they are able to retrieve cases of interest within their scope [6], yet the objective of this is not to evaluate the quality of retrieval [8]. The aim of the present study was therefore to evaluate the performance of four SMQs for retrieval of ADRs in the French pharmacovigilance database using a validated reference set of cases.

2 Methods

The study used data from the French Pharmacovigilance database for research (BNPV-R), which includes all reports entered in the *Base Nationale de Pharmacovigilance* (BNPV) between January 2000 and August 2010. The BNPV includes all ADRs reported to the 31 French regional pharmacovigilance centres by health professionals during this period, but not those reported to manufacturers. Since 2011, patients and approved patient advocacy groups may also notify any adverse effect suspected to be due to a drug [9].

Each regional pharmacovigilance centre reviews and medically assesses every case before entering the case into the BNPV. All ADRs are coded by each regional centre using MedDRA®. The associated coding related to the diagnosis or the description of symptoms is made by an expert in pharmacovigilance (medical doctor or pharmacist) in the 31 centres. MedDRA® coding procedures are followed by all coders of all centres, who are regularly trained by MSSO on coding with MedDRA®, and coders base their decisions on reference texts and guidelines [7, 10, 11].

The BNPV includes reports related to all drugs, including illicit drugs, herbal medicines, homeopathy and toxics, but the BNPV-R excludes these reports if such substances are the only ones suspected to be involved in the case. For this study, reports related to vaccines as the only suspected substances were not considered. The study presented here was performed using a subset for the year 2009.

[1] MedDRA® terminology is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). MedDRA® trademark is owned by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) on behalf of ICH.

[2] Since 1998, MedDRA® has been managed by the MSSO.

2.1 Event Selection

Four SMQs related to serious adverse events, "agranulocytosis", "demyelination", "osteonecrosis" and "psychosis", were selected to evaluate SMQ performance. These were chosen as they represent serious drug reactions related to different organs with both a wide-ranging number of PTs and a proportion of PTs in the broad search that are also in the narrow one: (i) the broad SMQ for "agranulocytosis" includes 76 PTs of which 16 % are also in the narrow search; (ii) the broad SMQ for "demyelination" includes 40 PTs, 85 % of which are in the narrow search; (iii) "osteonecrosis" includes 66 PTs, 6 % of which are in the narrow search; and (iv) "psychosis" includes 125 PTs, 63 % of which are in the narrow search.

2.2 Gold Standard

In order to evaluate the performance of SMQs, a reference set representing the gold standard was created. The official MSSO definition of the selected SMQs was used to create a list of English keywords related to each selected ADR. Thereafter, the keywords were translated into the French language, also taking into account abbreviations and acronyms used in daily practice by healthcare professionals. The list of keywords, and their French translation (with possible typographical errors) are reported in Electronic Supplementary Material 1. From the free-text section of the BNPV-R, these keywords were used to extract potential cases of each selected ADR. In order to select the gold standard reference set related to the above-mentioned ADRs, two authors (DA/BR or DA/AG), blinded to one another, evaluated the retrieved cases following an established set of criteria to ensure consistency (Electronic Supplementary Material 2). The selected cases were crosschecked and, in case of discrepancy, a third author (HG), an expert in case evaluation, made the final assessment. The set of validated cases constituted the gold standard.

2.3 Statistical Analysis

Reports retrieved through the SMQ search (narrow or broad search) were considered to be (i) true positives, if they had been included in the gold standard; or (ii) false positives, if they had not been included in the gold standard. Reports not retrieved through the SMQ search were considered to be (i) true negatives, if they had not been included in the gold standard; or (ii) false negatives, if they had been included in the gold standard. The performances of the studied SMQs in identifying cases of the events of interest were evaluated in terms of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). The calculations of these values were based on the 2×2 table presented in Table 1.

All values were presented as rates and the 95 % confidence intervals (CIs) of the estimators were carried out using SAS® v9.3 (SAS Institute, Inc., Cary, NC, USA).

3 Results

From January to December 2009, a total of 20,830 reported cases of ADRs were collected in the BNPV-R. Queries in the free-text narratives allowed the identification of 894 potential cases of agranulocytosis, 166 cases of demyelination, 91 cases of osteonecrosis and 630 cases of psychosis. Among these, we confirmed 337 cases as agranulocytosis (37 % of cases identified by free-text search), 17 of demyelination (10 %), 52 of osteonecrosis (57 %) and 230 of psychosis (37 %); these constituted the gold standard. For all of the SMQs tested, specificity and NPV were greater than 98 % for both narrow and broad searches (Table 2).

3.1 Agranulocytosis

The narrow SMQ for agranulocytosis found 453 potential cases, of which 212 were true positives; sensitivity was 62.9 % (95 % CI 57.5–68.1) and PPV was 46.8 % (95 % CI 42.1–51.5). The broad search found 487 potential cases of agranulocytosis, of which 213 were true positives; sensitivity was 63.1 % (95 % CI 57.7–68.3) and PPV was 43.6 % (95 % CI 39.2–48.2) (Table 2).

3.2 Demyelination

The narrow SMQ for demyelination found 44 potential cases, of which 15 were true positives; sensitivity was 88.2 % (95 % CI 63.6–98.5) and PPV was 34.1 % (95 % CI 20.5–49.9). The broad search found 46 potential cases, of which 16 were true positives; sensitivity was 94.1 % (95 % CI 71.3–99.9) and PPV was 34.8 % (95 % CI 21.4–50.3) (Table 2).

3.3 Osteonecrosis

The narrow SMQ for osteonecrosis found 66 potential cases of osteonecrosis, of which 49 were true positives; sensitivity was 94.2 % (95 % CI 84.1–98.8) and PPV was 74.2 % (95 % CI 62.0–84.2). The broad search found 93 potential cases of osteonecrosis, of which 49 were true positives; sensitivity was 94.2 % (95 % CI 84.1–98.8) and PPV 52.7 % (95 % CI 42.1–63.1) (Table 2).

Table 1 Calculation of sensitivity, specificity and predictive values of Standardised MedDRA® Queries in case identification

SMQ	Gold standard		
	Positive event	Negative event	
Positive event	*a* (TP)	*b* (FP)	PPV = $[a/(a + b)] \times 100$
Negative event	*c* (FN)	*d* (TN)	NPV = $[c/(c + d)] \times 100$
	Se = $[a/(a + c)] \times 100$	Sp = $[b/(b + d)] \times 100$	

FN false negative, *FP* false positive, *NPV* negative predictive value, *PPV* positive predictive value, *Se* sensitivity, *SMQ* Standardised MedDRA® Query, *Sp* specificity, *TN* true negative, *TP* true positive

Table 2 Performance of the selected Standardised MedDRA® Queries for the retrieval of cases

	Se (%) [95 % CI]	Sp (%) [95 % CI]	PPV (%) [95 % CI]	NPV (%) [95 % CI]
Agranulocytosis				
Narrow	62.9 [57.5–68.1]	98.8 [98.7–99.0]	46.8 [42.1–51.5]	99.4 [99.3–99.5]
Broad	63.1 [57.7–68.3]	98.7 [98.5–98.8]	43.6 [39.2–48.2]	99.4 [99.3–99.5]
Demyelination				
Narrow	88.2 [63.6–98.5]	99.9 [99.8–99.9]	34.1 [20.5–49.9]	99.99 [99.97–100.00]
Broad	94.1 [71.3–99.9]	99.9 [99.8–99.9]	34.8 [21.4–50.3]	99.99 [99.97–100.00]
Osteonecrosis				
Narrow	94.2 [84.1–98.8]	99.9 [99.9–100.0]	74.2 [62.0–84.2]	99.99 [99.96–100.00]
Broad	94.2 [84.1–98.8]	99.8 [99.8–99.9]	52.7 [42.1–63.1]	99.99 [99.96–100.00]
Psychosis				
Narrow	75.1 [69.0–80.6]	99.9 [99.8–99.9]	87.8 [82.3–92.0]	99.7 [99.6–99.8]
Broad	82.5 [77.0–87.2]	99.4 [99.3–99.5]	61.4 [55.7–66.8]	99.8 [99.7–99.9]

CI confidence interval, *NPV* negative predictive value, *PPV* positive predictive value, *Se* sensitivity, *Sp* specificity

3.4 Psychosis

The narrow SMQ for psychosis found 196 potential cases of psychosis, of which 172 were true positives; sensitivity was 75.1 % (95 % CI 69.0–80.6) and PPV was 87.8 % (95 % CI 82.3–92.0). The broad search found 308 potential cases of psychosis, of which 189 were true positives; sensitivity was 82.5 % (95 % CI 77.0–87.2) and PPV was 61.4 % (95 % CI 55.7–66.8) (Table 2).

4 Discussion

In the present study, performance varied among the SMQs tested: the best performance for case retrieval was obtained using SMQ osteonecrosis, whereas the worst was found with SMQ agranulocytosis.

As indicated in the *Introductory Guide for Standardised MedDRA® Queries*, a narrow search yields specificity while the broad search yields sensitivity [5]. However, due to the large number of reported ADRs collected in the BNPV, specificity and NPV values were close to 100 % for all tested SMQs, which limits their pertinence in the present study but also for evaluation of SMQ performance in other spontaneous reporting databases. Sensitivity and PPV were more informative, and, although sensitivity is favoured in pharmacovigilance [12], the choice of SMQ search should also consider a PPV that reflects the number of false positives and which affects the time taken to process cases. Interestingly, there was little difference in sensitivity between the narrow and broad searches of a given SMQ. This finding may be explained by the coding process used by medical staff in pharmacovigilance centres who are trained to code the most important medical events, which frequently correspond to the terms included in the narrow search; signs or symptoms are described in the free-text section and possibly coded, and these often correspond to the terms included in the broad search.

Among the four selected SMQs, the best performance was observed for osteonecrosis. This could be due to the characteristics of this condition, which is relatively simple to identify through clinical examination and imaging. Moreover, few diseases are considered in the differential diagnosis process and a relatively small number of drugs could induce this disease, such as corticosteroids or bisphosphonates [13]. There was, however, a markedly lower PPV for the broad search, which could be in relation to the number of PTs included. As sensitivity was equally good for both searches, the results suggest that the narrow SMQ should be employed, as the broad search will identify many

more false positives. The SMQ demyelination presented similar sensitivity in its broad search as that found for osteonecrosis, yet the PPV was particularly low, and equally so for both narrow and broad searches. This may be explained by the low number of cases retrieved for both events. This might also be due to the event definition for demyelination, which states that the lesion has to be confirmed by magnetic resonance imaging (MRI) examination, thus excluding reports of optic neuritis without such confirmation, for instance. Thus, either search type of this SMQ could be used for case retrieval (similar sensitivity and PPV), but a case-by-case analysis would be required to avoid the inclusion of many false positives (particularly low PPV). For psychosis, performance was relatively good for both searches, with a trend towards improved sensitivity for the broad search, although it was accompanied by a significant decrease in PPV. Performance for this SMQ was not as good as that obtained with demyelination or osteonecrosis SMQs, which could be explained by the characteristics of the disease. A psychiatric diagnosis is often complicated and may be controversial, as illustrated by the permanent update of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), now at its 5th version [14]. Consequently, the coding could be considered more complicated and controversial, with a higher possibility of error than for other reactions; the data presented here support the use of the narrow search, as the PPV is significantly better than that of the broad one. Finally, the worst performance was found for agranulocytosis. The low sensitivity could be related to difficulties in distinguishing agranulocytosis from neutropenia, which is not included in the definition of the SMQ [5]. For example, a case could be reported by the physician as that of neutropenia, but the white blood cell count reported in the free text is compatible with agranulocytosis (i.e. absolute neutrophil count of $<500/mm^3$). Thus, if the PT "neutropenia" was used (instead of agranulocytosis), this could have led to a number of false positives. Better sensitivity could be achieved by inclusion of neutropenia in the SMQ agranulocytosis but this would increase the number of false positives, which is of particular importance as the PPV of the current SMQ (both searches) was found to be low. To limit the risk of misclassification, it may also be proposed that the SMQ agranulocytosis be replaced by a SMQ neutropenia, or possibly to identify other terms that may be added or combinations of terms that provide better results [15–18].

Taken together, differences in SMQ performance seem to be related to the characteristics of the disease of interest and this should be taken into consideration when using SMQs for case retrieval. Performance of SMQs based purely on phrases might be expected to be higher than performance of SMQs based on a numeric threshold, given an increased risk of misclassification. Similarly to SMQ agranulocytosis, "false positive" cases may be expected to occur in any ADR for which diagnosis is based on a numeric threshold of a laboratory test. Conversely, good performance can be expected among SMQs that deal only with ADRs described through phrases and that are relatively simple to identify.

Limitations inherent to this study include the relatively limited number of SMQs selected, with regard to the 94 currently existing in version 16.1 of the list of SMQ topics [19]. However, those that were chosen relate to different system organs and took into account the diversity of SMQs, which, as discussed above, is likely to explain the heterogeneous performance found. Another potential limitation is the risk of provisional diagnosis or wrong diagnosis, but this concerns every drug safety database and numerous ADRs, and does not explain the heterogeneity between the tested SMQs. Furthermore, MedDRA® coding procedures specify that in cases of provisional diagnosis, signs and symptoms (if known) must also be coded [20]. In addition, it should be noted that we used SMQ version 15.0, although MedDRA® version 12.1 was used in the database in 2009. However, when comparing the syntaxes of the SMQs for these versions, no major change was observed. Thus, we preferred to use the newest SMQ version, as the versions are supposedly improved over time. Furthermore, the changes in MedDRA® almost exclusively concern marginal terms related to signs and symptoms, which are not usually used by French pharmacovigilance staff members who code diagnoses more than signs and symptoms.

Regarding the generalisation of the results to other SMQs, further research is needed, particularly with regards to the performance of SMQs for frequently occurring ADRs that were not evaluated here as we focused on serious events. It would, however, be interesting to have data on the performance of such SMQs, but owing to the frequency of cases retrieved it may be useful to perform such studies on a randomly selected subset of the ADR database. Additionally, we did not test any of the eight SMQs with an algorithmic feature (such as "anaphylaxis" or "neuroleptic malignant syndrome") and therefore the results may not be applicable to such situations. Regarding the generalisation to other databases, the ability of SMQs to retrieve cases will be influenced by the characteristics of the dataset; for instance, coding conventions may affect the pertinence of broad SMQs [21]. Although the coding by the pharmacovigilance experts (trained in MedDRA® coding) could be considered to be accurate, its appropriateness is obviously improvable. Based on this study, future investigations could focus on false negative events, reasons for misclassification, and the appropriateness of coding for each term recorded in the database.

5 Conclusion

This study found heterogeneous performance of SMQs for case retrieval, and the results suggest that sensitivity will be adversely affected for diseases that are characterised by a numerical value. Therefore, it could be expected that for other SMQs, with the possible exception of those with algorithmic functions, performance may be affected in the same manner. This needs to be verified by future investigations, but from a pragmatic standpoint, caution should be employed when using SMQs that relate to a diagnosis based on a threshold.

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