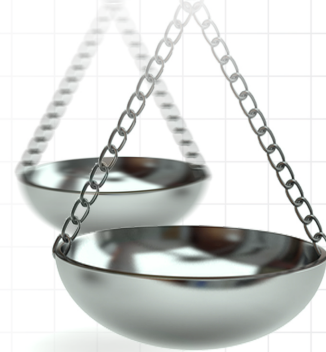




Patient-relevant outcomes associated with generic tamsulosin, levothyroxine and amphetamine in the FDA Adverse Event Reporting System: a pilot study

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Aim: Patient-reported outcomes associated with adverse events (AEs) reported with generics have not been evaluated. To map AEs associated with generics to the NIH Patient-reported Outcomes Measurement Information System. **Methods:** We mapped 381 AEs from 148 case reports of generic tamsulosin, levothyroxine and amphetamine/dextroamphetamine to the physical, mental and social domain of the NIH Patient-Reported Outcomes Measurement Information System after reviewing 1237 case reports in the US FDA's Adverse Event Reporting System (FAERS; 2011–2013). **Results:** 75%, 76% and 71% reports were classified under the physical domain for tamsulosin, levothyroxine and amphetamine/dextroamphetamine, while 9%, 9% and 18% reports were classified under the mental domain, respectively. **Conclusion:** FAERS reveals several domains of patient-relevant concerns associated with generic drugs.

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Keywords: amphetamine • FAERS database • levothyroxine • patient-relevant outcomes • PROMIS outcome • tamsulosin

Generic drugs are widely used in the USA and accounted for 88% of all prescriptions dispensed in the USA in 2015 [1]. However, patients express concern about the effectiveness and safety of generic drugs and report adverse experiences with their use [2,3]. We sought to describe the adverse events (AEs) attributable to generic drugs that are being reported to the US FDA Adverse Event Reporting System (FAERS) and to assess the value of classifying these reports using a patient-centered framework. At times, this may help investigators, regulators and manufacturers to better understand what impact these AEs are having on patients.

The patient-relevant outcome reflects the concerns of the patient about a disease condition or the treatment effects. It would be helpful to visualize the change in health-related quality of life and gives a fair idea for the prescriber to evaluate the cause for treatment dissatisfaction and medication nonadherence [4].

In 2009, FDA finalized and issued a guidance to use patient-reported outcomes to support labeling claims [5]. In the future, patient-relevant concerns about the drugs could be of potential value for regulatory authorities for updating the drug label.

The FAERS received more than one million spontaneous adverse event reports from consumers, physicians and manufacturers from 2012 to 2014 [6]. Postmarketing AEs and medication errors are coded with Medical Dictionary for Regulatory Activities (MedDRA), which uses a multiaxial hierarchical structure. MedDRA, however, does not allow one to distinguish easily between patient-relevant concerns and those that are less relevant – these might be transient abnormalities in a laboratory measure or a medication dosing error that had no impact on the patient. The objective of this study was to understand the patient-relevant concerns associated with generic drugs in FAERS.

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Methods

Study design & data source

The FAERS is the US passive surveillance system for medication AEs. These reports are submitted voluntarily by healthcare providers, consumers and manufacturers. The publicly available data in FAERS include seven data tables with information about patient demographics, drug or biological product name, adverse event, patient outcome, the source of the report, drug therapy start and end date and indication for use of the reported drug. AEs and medication errors are coded by FDA staff and contractors using MedDRA terms.

Selection of drugs

For this study, we selected three drugs: tamsulosin, levothyroxine and amphetamines/dextroamphetamine. Levothyroxine was selected because of its relatively narrow therapeutic index and known patient and clinician concerns about the use of the generic product. The indications for the three drugs are very different suggesting that we might see a broad range of patient-relevant outcomes. Finally, during the study period between 2011 and 2013, generic tamsulosin and amphetamine/dextroamphetamine came to market after patent expiration of the brand products.

Inclusion/exclusion of case reports

We identified all case reports with tamsulosin, levothyroxine and amphetamine/dextroamphetamine as the primary suspect drug reported to FAERS between 2011 and 2013. We required that the case reports included complete information on age, sex, suspected drug name and the adverse event.

In an earlier study, we developed and validated an algorithm to identify generic drugs in publicly available FAERS and assessed the accuracy of the algorithm by comparing the results to the detailed source narratives obtained from the FDA via the Freedom of Information Act [7]. This algorithm classified the suspected drug as definitely generic, probably generic, brand or unclassifiable using the name of the manufacturer, new drug approval number and presence of the word 'generic' mentioned verbatim in the variable listing drug. For the present study, we used only the reports in FAERS associated with drugs classified as 'definite' and 'probable' generic drugs.

Selection of a patient-relevant outcomes framework

We reviewed citations in PubMed to identify patient-centered frameworks used to classify drug-associated AEs. We adapted the schema used by National Institute of Health Patient-Reported Outcomes

Measurement Information System (NIH-PROMIS®, MD, USA). PROMIS is a set of patient-centered measurement tools that can be used to evaluate and monitor physical, mental and social health [8]. We selected the NIH-PROMIS framework because we did not identify any other existing framework specifically for mapping spontaneously reported AEs.

The NIH-PROMIS classifies measures or tools according to profile domains. These include the global health domain, physical health domain, mental health domain and social health domain. The overall global health domain reflects the overall health of an individual. The physical domain is further classified into symptoms and functional ability, mental domain into affect, behavior, cognition and social domain into relationships and function. The items in the physical health domain capture physical function such as pain, fatigue and sleep disturbances, sexual symptoms, gastrointestinal symptoms and shortness of breath and functional disability such as gait disturbance. The physical domain is further subdivided into the subdomains of symptoms and functions. The mental health domain captures symptoms such as anxiety, depression, anger, substance abuse, alcohol, psychosocial impact and self-efficacy, behavioral symptoms such as suicidal ideation, homicidal ideation, completed suicide and cognitive function such as confusion and disorientation. The mental health domain is further subdivided into the subdomains of affect behavior and cognition. The social health domain captures the ability of the respondent to participate in social and family activities. The social health domain is further subdivided into the subdomains of functions and relationships. Many of the domains of the NIH-PROMIS framework have been prospectively validated in multiple patient populations [9–11].

Mapping AEs onto NIH-PROMIS domains

We mapped the AEs associated with generic drugs identified in FAERS onto the existing domains and associated subdomains of the NIH-PROMIS framework. One reviewer examined MedDRA coded AEs (serious and nonserious) associated with generic drugs from FAERS and classified them as belonging to one or more of the NIH-PROMIS profile domains and subdomains. The classification of AEs under NIH-PROMIS domains were validated with clinical information from the case narratives obtained from FDA under the Freedom of Information Act request. A second reviewer with methodological and clinical expertise adjudicated the classification. Data extraction forms were pilot tested prior to implementation. Our unit of analysis was an adverse event; a single case report could include more than one adverse

drug reaction. In such cases, each adverse event was classified individually.

For the purpose of this study, we describe a patient-reported outcome using the FDA's definition: "Any report of the status of a patient's health condition that comes directly from the patient, without the interpretation of patient's response by a clinician or anyone else" [5]. However, since FAERS includes reports from health professionals and manufacturers, we expanded our scope beyond patient-reported outcomes to patient-relevant outcomes. We relied on the NIH-PROMIS framework along with expert judgement to identify patient-relevant outcomes. Patient-relevant outcomes include a wide range of symptoms affecting physical, mental and social health. While for the most part, patient-relevant outcomes overlap with patient-reported outcomes, they do not necessarily have to be reported by patients and could be reported by health professionals or manufacturers. We relied on the clinical information obtained from the narratives to map the AEs onto PROMIS domain. Physical symptoms that were considered patient-relevant, included pain, fatigue, gastrointestinal symptoms, sleep-related disorder and mental health included anxiety, depression and suicidal tendency. Social symptoms included withdrawal from social activities.

We deliberated around the inclusion of certain surrogate outcomes as patient-relevant outcomes. The outcomes where linkages to clinical outcomes have been well established were considered patient relevant, such as elevated blood pressure. In contrast, laboratory markers of disease such as hyperglycemia were not considered patient-relevant, although they may be of consequence. We also excluded other asymptomatic laboratory markers such as hypercalcemia in which patients and/or other reporters only reported on markers of disease without associated symptoms or clinically relevant outcomes. A representation of the overlap between the patient-relevant outcomes and patient-reported outcomes is shown in [Figure 1](#).

Results

We included 148 generic reports out of 1237 case reports in the analysis ([Figure 2](#)). The demographic characteristics of the participants including their age, sex and source of reports are described in [Table 1](#). There were differences in the proportion of AEs that were reported by patients for the three drugs. Only 28% of the AEs associated with stimulants were reported by patients, whereas patients reported more than 75% of the AEs with the other two drugs.

Among these reports, 381 AEs were related to generic drug use; 77 AEs from 39 reports were attributed to

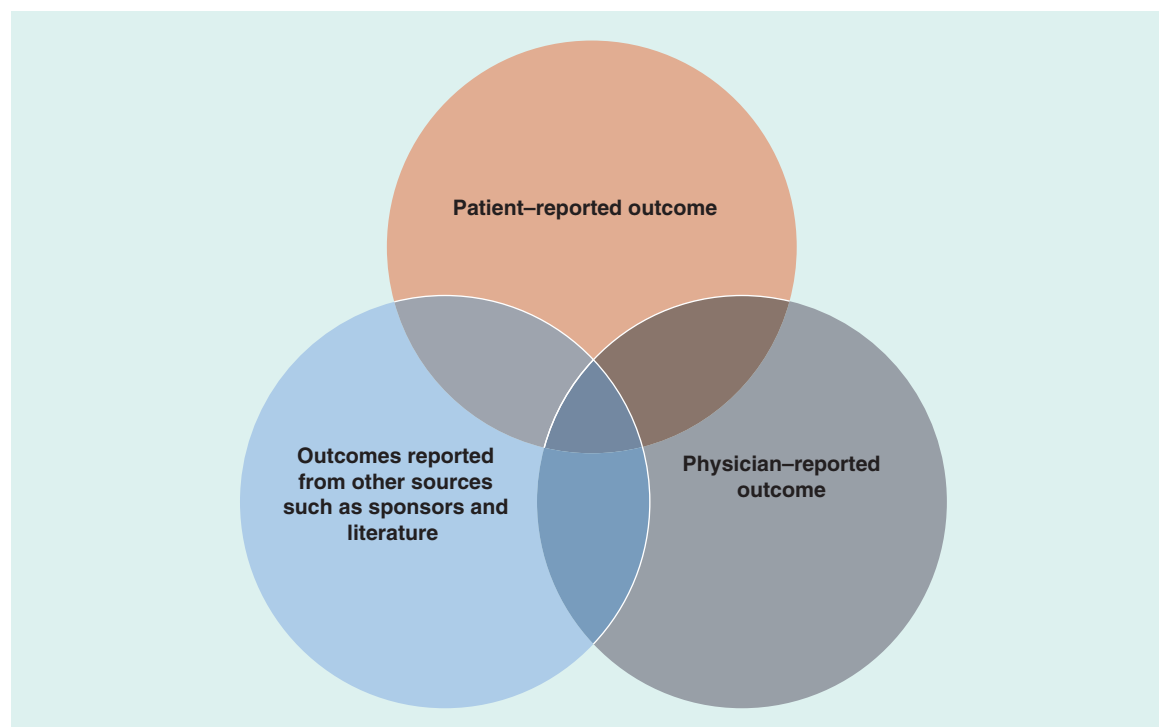


Figure 1. Relationship between patient-relevant and patient-reported outcomes. Inclusion criteria for patient-relevant outcomes: (1) symptoms reported by patient, (2) signs elicited by physicians, (3) clinical events. Exclusion criteria for patient-relevant outcomes: (1) abnormal lab values without symptoms (e.g., hyperglycemia and hypercalcemia), (2) medication error, (3) product quality issues.

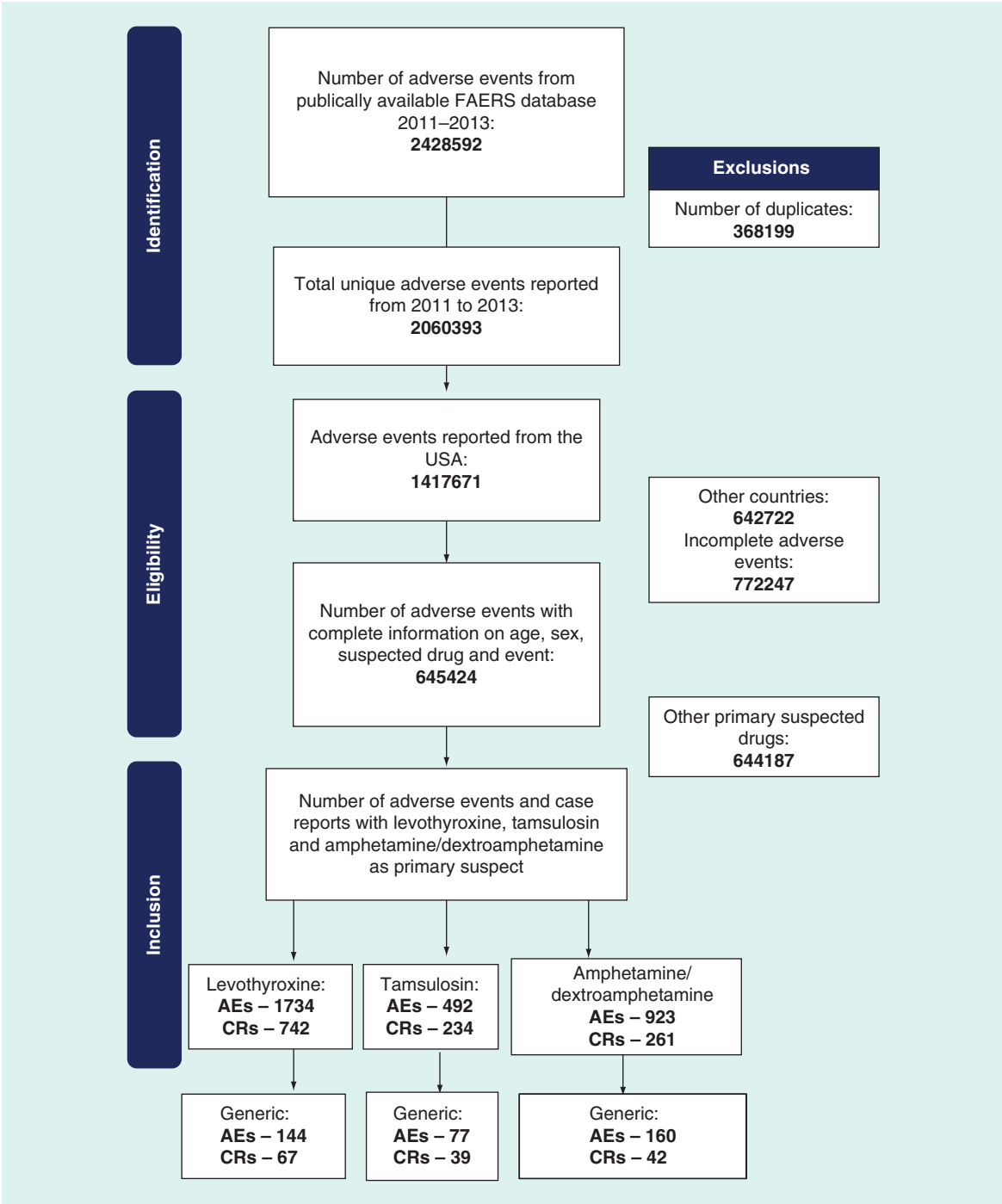


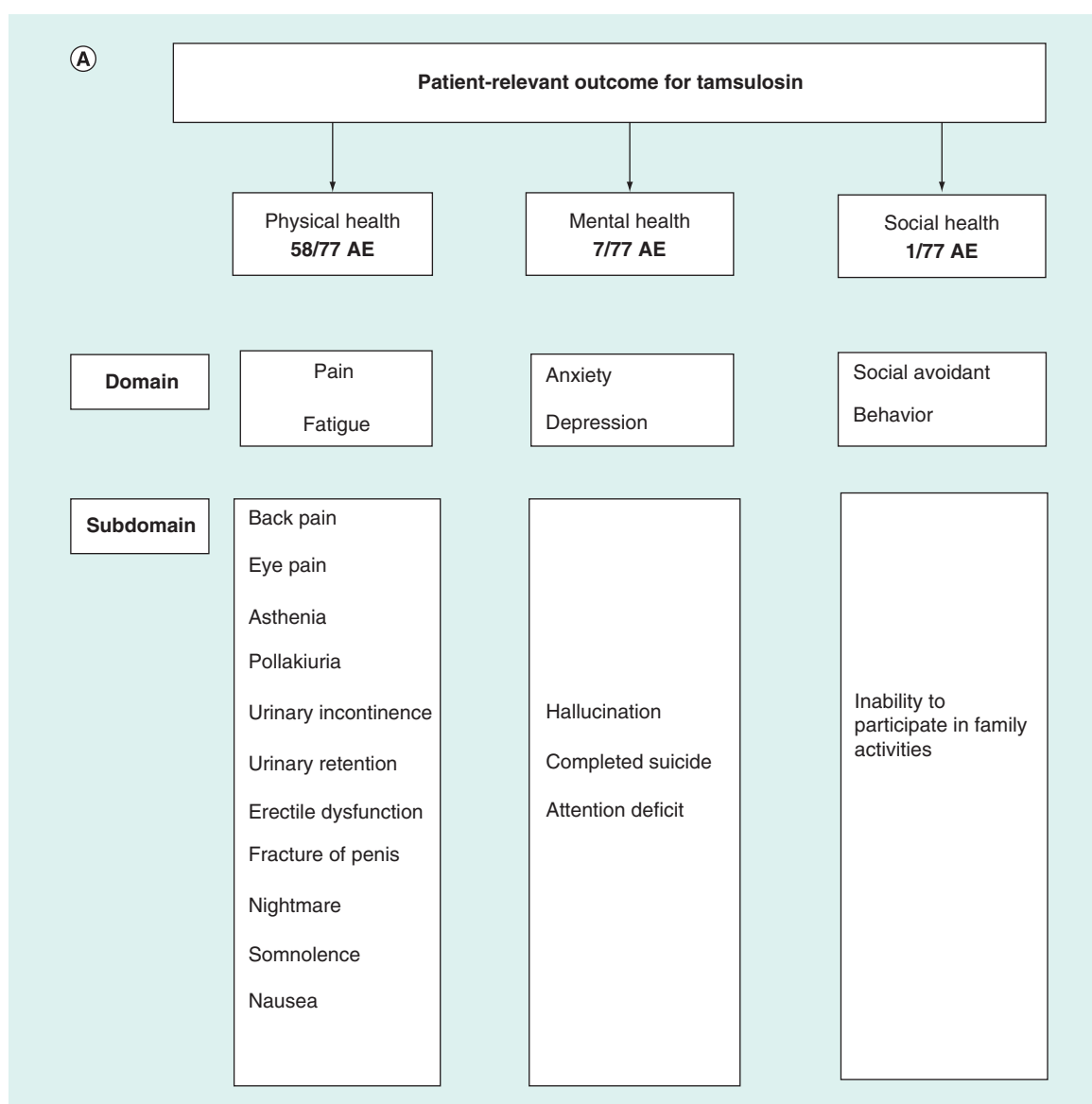
Figure 2. Flow diagram for selection of case reports from FAERS. The flow diagram shows the identification of 148 generic case reports from the FAERS database after applying the inclusion and exclusion criteria. 148 generic case reports include 67 case reports of tamsulosin, 39 case reports of levothyroxine and 42 case reports of amphetamines/dextroamphetamine. AE: Adverse event; CR: Case report; FAERS: Food and Drug Administration’s Adverse Event Reporting System.

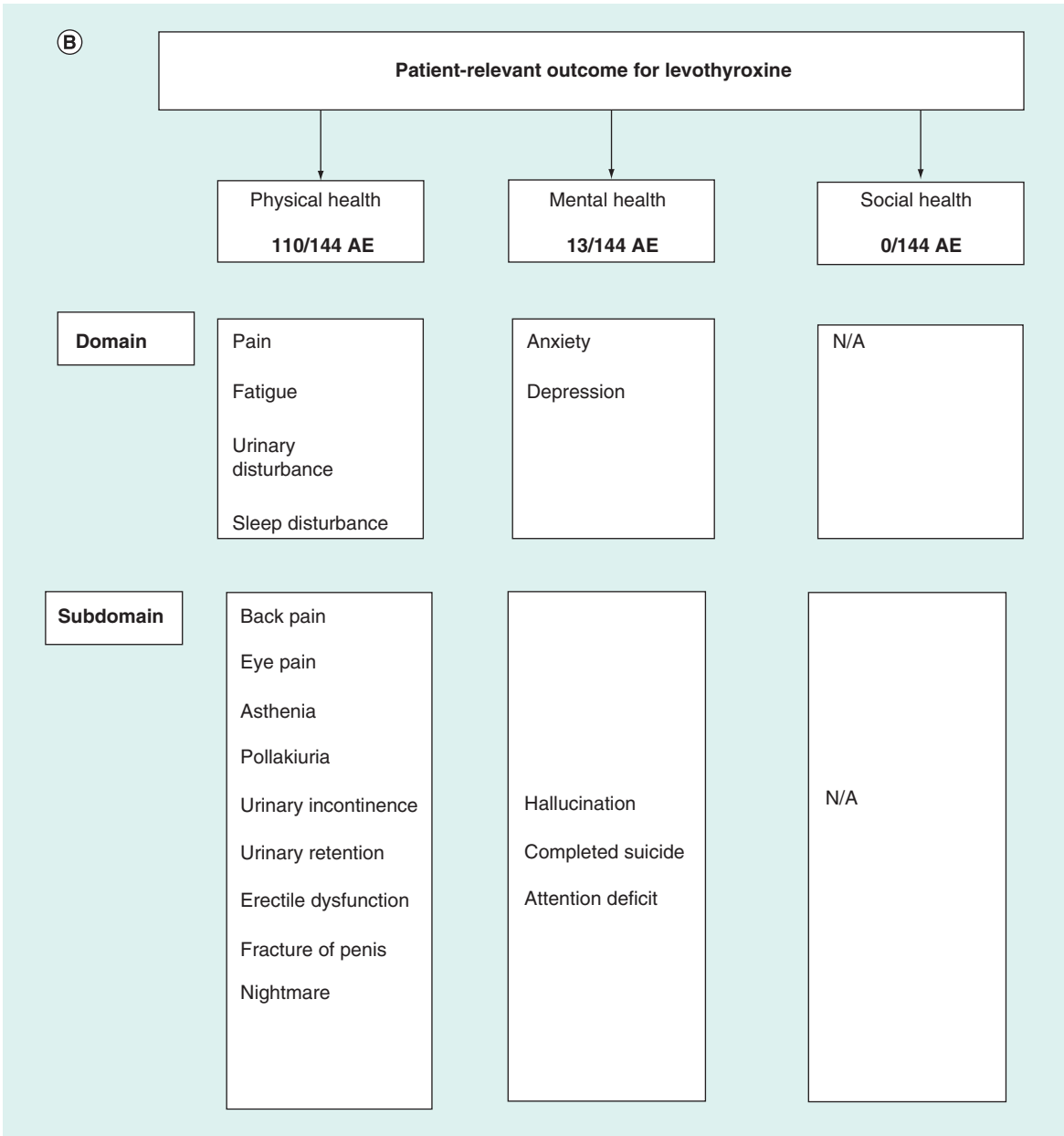
tamsulosin, 144 AEs from 67 reports were attributed to generic levothyroxine and 160 AEs from 42 reports were attributed to amphetamine/dextroamphetamine. The majority of AEs associated with generic drugs could be mapped onto the NIH-PROMIS domain

using publicly available FAERS data (n = 295) which is shown in the [Figure 3A, B & C](#). An additional 39 AEs could be mapped onto the NIH-PROMIS domains only after we reviewed the detailed narratives obtained from the FDA. 52 AEs could not be classified either

Table 1. Descriptive analysis of the reports extracted from FDA's Adverse Event Reporting System from 2011–2013.

Demographic Characteristics	Tamsulosin (n = 39 reports)	Amphetamines/ dextroamphetamines (n = 42 reports)	Levothyroxine (n = 67 reports)
Age, median (range)	72.7 years (42–101 years)	33.8 years (8 months–75 years)	56.3 years (11–98 years)
Males (%)	100	61.9	11.9
Occupation of the reporter (%):			
– Consumer	30 (77%)	12 (29%)	52 (77%)
– Physician	4 (9 %)	19 (45%)	1 (2%)
– Pharmacist	3 (8%)	1 (2%)	6 (9%)
– Other healthcare professional	1 (3%)	8 (19%)	1 (2%)
– Missing	1 (3%)	2 (5%)	7 (10%)





due to inadequate clinical information or they were not considered to be patient-relevant.

The majority of AEs mapped to the physical health domain for all three generic drugs when we used data from the publicly available FAERS. Among the 77 AEs associated with generic tamsulosin, 53 (69%) were grouped under physical, eight (10%) under mental, one (1%) under social domains and 15 (20%) were unclassifiable. Out of 144 AEs associated with levothyroxine, 92 (64%) were mapped under physical, 16 (11%) were mapped under mental 2 (1%) under social domains and 34 (24%) were unclassifiable. Similarly, out of 160 AEs associated with amphetamine/dextroamphetamine, 83 (52%) were

grouped under physical, 38 (24%) under mental and 2 (1%) were grouped under the social domain and 37 (23%) were unclassifiable.

After including information from the detailed narratives sent by the FDA, we found that some of the adverse AEs could be reclassified which is shown in [Figure 4A, B, C & Table 2](#).

Discussion

We classified AEs associated with three different generic drugs into the physical, mental and social domains and the subdomains of the NIH-PROMIS framework. The majority of reports had AEs that could be classified as physical or mental concerns,

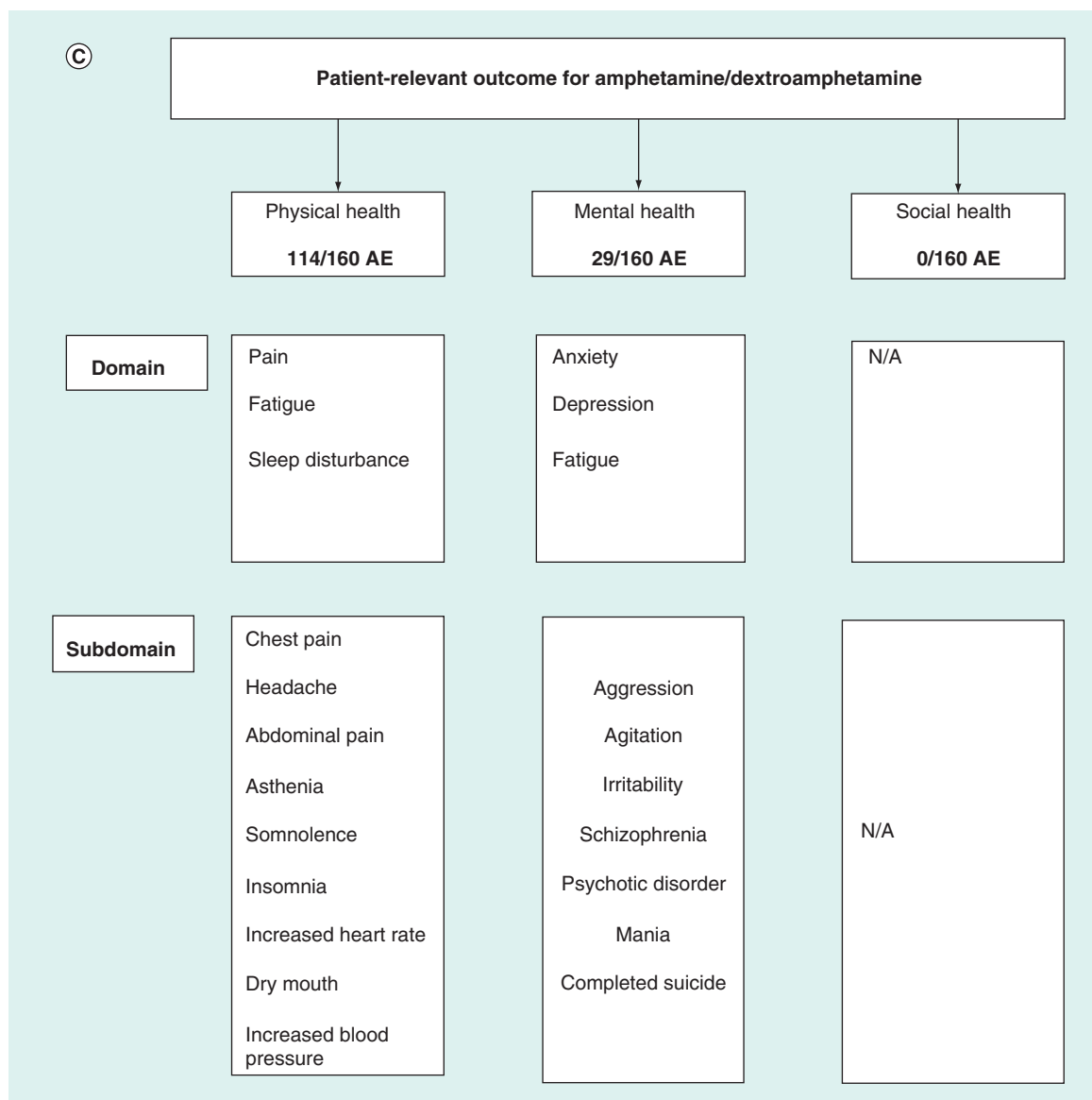


Figure 3 (see previous two pages). Mapping of adverse events onto NIH-PROMIS domains. Adverse events associated with generic (A) tamsulosin, (B) levothyroxine and (C) amphetamine/dextroamphetamine classified as patient-relevant outcomes under physical, mental and social health domains under the PROMIS framework. AE: Adverse event; N/A: Not applicable; PROMIS: Patient-Reported Outcome Measurement Information System.

although, there were differences among the three classes. Very few reports included data on social concerns. We also identified a number of reports that we classified as not being patient-relevant and others that could not be classified due to incomplete data.

There was a wide spectrum of patient-relevant concerns reported with each of the generic drugs in various domains and subdomains of the NIH-PROMIS framework. Patient-relevant concerns in the mental health domain and subdomain for amphetamine/dextroamphetamine may reflect the underlying indication for the drug. In the social health domain, socially

avoidant behavior was reported only with tamsulosin. There were no reports in the social domain with amphetamine/dextroamphetamine or levothyroxine.

There are few studies that have evaluated how AEs associated with generic or brand name drugs may be mapped to patient-relevant concerns. Banerjee *et al.* argue that the reporting of AEs can be more effective when reported as patient-reported outcomes [12]. These researchers advocate for The Patient-Reported Outcome Measures in Safety Event Reporting Consortium which was set up to capture patient-reported outcomes of AEs in order to improve safety event

reporting. This UK-based consortium includes industry, regulatory authority, academic and the private sector and patient representatives who are interested in the area of patient-reported outcomes of AEs. It is thought that patient-reported outcomes better capture the intensity of the AEs and is helpful when

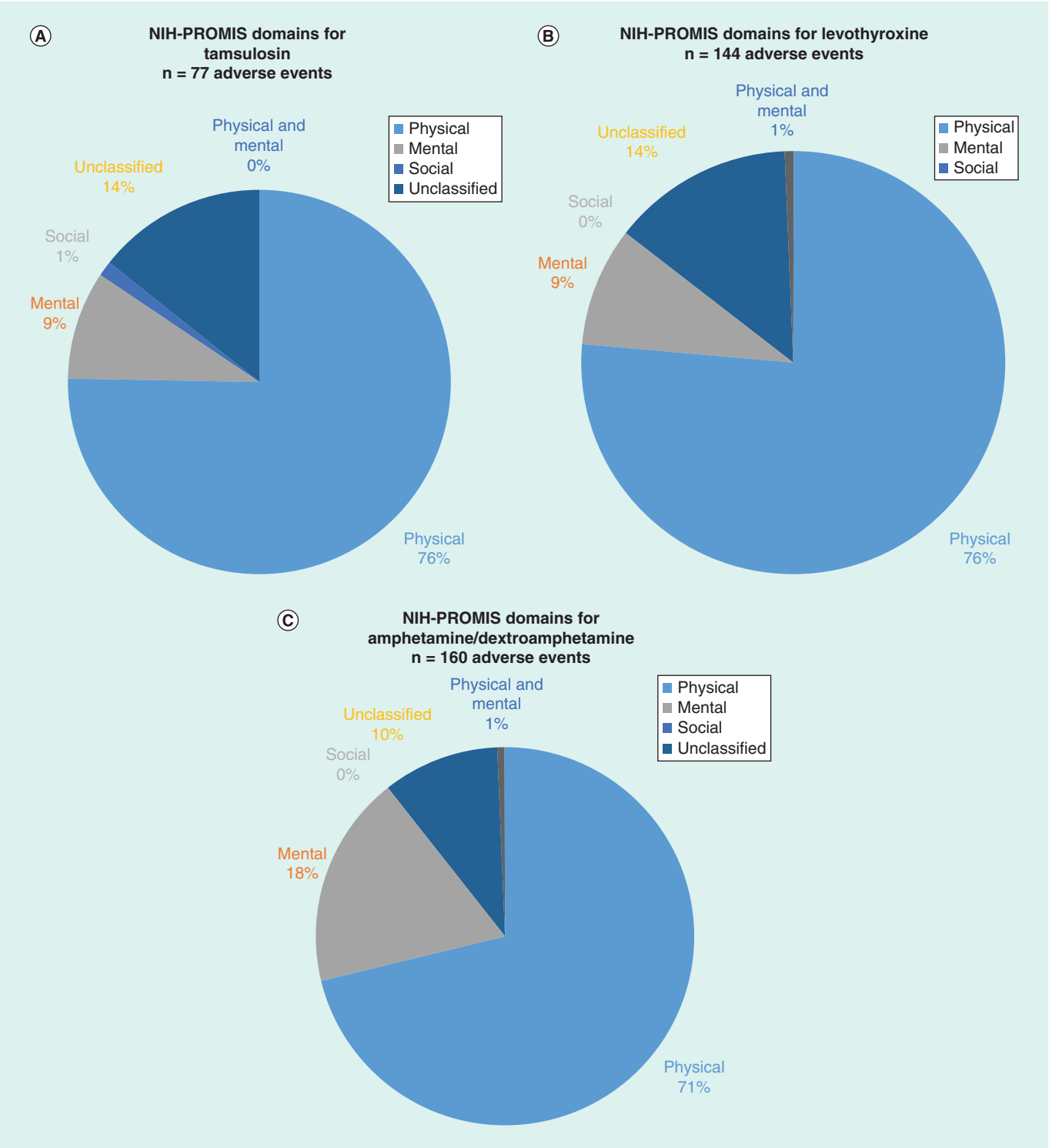


Figure 4. NIH-PROMIS domains for (A) tamsulosin, (B) levothyroxine and (C) amphetamine/dextroamphetamine. Pie chart depicts the percentage of adverse events associated with generic tamsulosin classified under physical health, mental health, physical and mental health and social health domains along with the percentage of adverse events that remain unclassified. NIH-PROMIS: National Institute of Health Patient-Reported Outcomes Measurement Information System.

Table 2. Description of the analysis of the reports onto the physical mental and social subdomains of the NIH-PROMIS.

Generic drugs	Physical domain, n (%)		Mental domain, n (%)			Social domain, n (%)		Unclassified, n (%)	Total number of AEs
	Symptom	Function	Affect	Behavior	Cognition	Function	Relationship		
Tamsulosin	55 (72%)	3 (4%)	4 (5%)	2 (3%)	1 (1%)	0	1(1%)	11(14%)	77
Levothyroxine	103 (72%)	3 (2%)	9 (6%)	5 (3%)	0	0	0	24 (17%)	144
Amphetamine /dextroamphetamine	102 (63.5%)	6 (4%)	16 (10%)	12 (8%)	1 (0.5%)	0	0	23 (14%)	160

AE: Adverse event; PROMIS: Patient-Reported Outcomes Measurement Information System.

regulators are balancing the benefits and risks of a marketed drug [13].

Our study was not designed to assess causal relationships or detect differences in patient-relevant concerns between generic and brand name drugs. Many studies have reported that clinical outcomes of the brand drugs are similar to their generic equivalents [14–17]. One of the prevalent patient-relevant concerns noted in the FAERS reports were allergic reactions which are conceivably due to the difference in drug excipients [18].

There are several similarities and differences between our approach to mapping AEs from FAERS onto the NIH-PROMIS and the Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PROCTCAE) [19]. PROCTCAE aims to integrate the experience of the patients into clinical trial adverse event reporting. For example, to understand the perspective of patients enrolled in cancer clinical trials, Kluetz *et al.* collected patient-reported AEs associated with the study drugs using a questionnaire [20]. The information obtained from the patients should help clinicians, to make a patient-centered benefit versus risk assessment about the use of the cancer therapy. In contrast to the PROCTCAE methodology, our approach allows the inclusion of outcomes reported from additional sources beyond patients such as manufacturers and physicians.

Our approach has some limitations that are largely due to the quality of reported data. Although, we used a valid and reliable algorithm to identify generic drugs, some amount of misclassification is always possible so that these reports may have included reports about some brand products too [7]. While we retrospectively applied the NIH-PROMIS framework for mapping spontaneously reported AEs in FAERS, our findings must be interpreted with caution because the PROMIS framework was developed for prospective collection of patient-reported outcomes.

Our analysis was limited by the incompleteness

in reporting and nonrepresentativeness of data in FAERS. The relative proportions of reports in various domains should not be misconstrued as evidence of the relative frequency of occurrence of such concerns because of the nonrepresentative nature of FAERS.

Despite these limitations, our study has several strengths. We used a reliable method to identify generic drugs using both publicly available FAERS and the detailed narratives and mapped three drugs onto the most widely used NIH-PROMIS domains. AEs reported to FAERS are currently classified by the MedDRA hierarchical system. While this allows examination of the data by System Organ Class, MedDRA terms may not fully capture the extent of patient-relevant concerns. We have outlined the feasibility of mapping AEs associated with generic drugs onto a framework of patient-relevant outcomes. This may allow end-users, such as policy makers, clinicians and regulators to judge whether generic drugs are associated with specific domain effects, such as physical health domain, beyond their individual adverse effects. Further replication of this approach using other generic and brand name drugs by other investigators is needed. However, future studies should evaluate how the mapping of AEs as patient-relevant outcomes may differ between brand name and generic drugs.

Conclusion

Our qualitative approach represents an initial step to mapping AEs associated with three generic drugs in FAERS onto the framework of patient-relevant outcomes using the NIH-PROMIS framework. These findings needed to be replicated in future studies comparing other generic drugs with brand name drugs. Such studies should further evaluate the internal reliability, test–retest reliability and face validity of classifications of AEs as patient-reported outcomes. Ensuring the completeness of reporting in reporting of AEs in FAERS will be helpful in achieving these goals.

Financial & competing interests disclosure

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discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

This study received an expedited review from the Johns Hopkins Medicine Institutional Review Board and from the FDA's Research Involving Human Subjects Committee. This study was conducted according to a prespecified protocol available upon request.

Summary points

- Patient-relevant concerns about generic drugs have been a long-standing concern for patients, physicians and policymakers. Previous efforts have focused on evaluating patient-relevant concerns about generics in the context of focus groups, questionnaires or administrative database studies.
- Data reported during postmarketing surveillance provides a unique opportunity to understand patient-relevant concerns associated with generic drugs.
- Our novel approach to classifying adverse events (AEs) associated with generic drugs in the FDA's Adverse Event Reporting System into the physical, mental and social domains of the National Institute of Health Patient-Reported Outcomes Measurement Information System framework allows physicians and policy makers to get a visual image of the relative domains of patient-relevant concerns associated with generic drugs.
- On evaluation of 381 AEs from 148 case reports associated with generic tamsulosin, levothyroxine and amphetamine/dextroamphetamine, most of the AEs were classified under the physical domain (75% for tamsulosin, 76% for levothyroxine and 71% for amphetamine/dextroamphetamine), followed by the mental domain (9.0% for tamsulosin, 9% for levothyroxine and 18% for amphetamine/dextroamphetamine).
- Very few AEs were classified under the social domain. Approximately, 13% of AEs could not be mapped under any of the domains because they were not patient-relevant or lacked clinical information.
- Future efforts to improve the completeness of reporting in Food and Drug Administration's Adverse Event Reporting System will improve our understanding of patient-relevant concerns associated with other generic and brand name drugs.

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