CLINICAL TRIALS

Gender differences in clinical registration trials: is there a real problem?

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AIMS

Several studies have reported the under-representation of women in clinical trials, thereby challenging the external validity of the benefit/risk assessments of launched drugs. Our aim was to determine the extent to which women have been included in clinical trials used for drug registration and to analyse the fraction of women participating in phases I, II and III.

METHODS

We conducted cross-sectional, structured research into publicly available registration dossiers of Food and Drug Administration (FDA)-approved drugs that are prescribed frequently. Furthermore, we analysed compounds with high hepatic clearance and a known gender-related difference in drug response. In a sensitivity analysis, we compared figures with US disease prevalence data.

RESULTS

For 38 of the initial 137 drugs (28%), sufficient data were reported and publicly available. For these drugs, 185 479 trial participants were included, of whom 47% were female and 44% were male; gender was not reported for 9% of participants. However, the number of female participants varied with the phase of the trial, with 22% females in phase I trials *vs.* 48% and 49%, respectively, in phase II and III trials. When compared with US disease prevalence data, 10 drugs (26%) had a greater than 20% difference between the proportion of females affected with the disease compared with representation in clinical trials.

CONCLUSIONS

From these publicly available data, there was no evidence of any systematic under-representation of women in clinical trials.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Several studies have reported under-representation of women in clinical trials, thereby challenging the external validity of benefit/risk assessments of launched drugs.
- Physiological differences in women and the presentation of disease symptoms may give rise to differences in the clinical outcome of medications. Therefore, it is paramount to evaluate the inclusion of women in clinical trials of newly approved drug molecules, and the possible effect size variation, for a proper regulatory review.

WHAT THIS STUDY ADDS

- A structured, cross-sectional review of publicly available registration data of clinical trials at the Food and Drug Administration was performed for the most frequently prescribed drug classes.
- No evidence was found of any systemic significant under-representation of women in clinical trials.
- During the clinical development phase, the proportion of women participating in trials increased gradually, from 22% in phase I to over 48% for phase II/III trials.

Introduction

The lack of gender and racial diversity in clinical trials has long been a matter of controversy. Traditionally, studies have been carried out in predominantly Caucasian countries, using mainly adult white males, especially for phase I clinical trials investigating tolerability, clinical pharmacology, dose-related side effects and early evidence of efficacy [1]. Historically, women of child-bearing age have been discouraged from participation in phase I trials because of undue risk to fetal development, especially after the thalidomide scandal of the 1960s [2]. This approach seems plausible and responsible in early clinical drug development, to avoid teratogenic effects in studies of compounds of which the vast majority will never reach the market anyway. However, public pressure has spurred detailed research on the participation of women in clinical drug trials, with an emphasis on later-stage studies – i.e. phase II and III trials.

In an analysis of new drug applications (NDAs) submitted in the 1980s and 1990s, it was shown that women were under-represented for analysis of some of these drugs [3]. Subsequently, in 1993, the Food and Drug Administration (FDA) published the Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs [4]. This guideline called for increased participation of females in clinical studies, and for gender-specific analysis to discern in greater detail any gender difference in drug effect(s). In 2001, an updated analysis revealed that in 36 NDAs that were granted FDA market authorization, the proportion of female participants had increased [4, 5]. In the latter US General Accounting Office report [5], across all the clinical trials, 52% of the study participants were women, 39% were men and 9% percent were not identified by gender. Meinert *et al.* performed a detailed analysis of the composition of study populations in reported clinical trials and argued that the idea that women were under-represented in clinical trials was exaggerated [6]. The analysis showed that in the period 1966–1975, a combination of male/female participants was present in 41% of trials, and this had increased to 55% over the period 1996–1998. A subsequent analysis comprised a review of all 724 clinical trials published in five major journals in 1985, 1990 and 1995. These trials were analysed for the numbers of female/male participants, and showed that the total percentage of female participants was 60%, and the percentage of women in mixed-gender trials

was approximately 40%. It can thus be concluded that women have been involved in the majority of clinical trials since the 1960s, even if the ratio has not been equal. Importantly, women-only studies were over-represented in cancer studies, even when excluding prostate and breast cancer [6].

Although this study showed that a large percentage of studies have been performed with a more or less equal mix of participants, the numbers of participants in these studies may not have been sufficient to result in enough power to discern any gender differences in outcomes accurately [6]. This question was specifically addressed for NIH-funded research [7]. Analysis of these trials showed that mixed-gender trials had an even mix of male (49%) and female (49%) participants. For all studies, including male-only and female-only trials, 57% of trial participants were female, 42% were male and 1% were of unknown gender. This, again, suggests an even distribution between male and female participants, at least for the NIH-funded research [7]. Recently, Cochrane meta-analyses were conducted to investigate gender-based subgroup differences in randomized controlled trials (RCTs) [8]. In the latter study, a total of 311 RCTs, 162 including both genders, 46 with males only, 103 with females only, were analysed, of which only 9% had a statistically significant gender–treatment interaction; this led the authors to conclude that these interactions occurred only slightly more frequently than would be expected by chance.

By contrast, several other studies have reported an under-representation of females in clinical trials (e.g. cancer, vascular surgery and cardiovascular trials [9–13]), with the general media continuing to report that large gender gaps are still putting women at a disadvantage [14]. This reporting has had serious effects on policy, with large amounts of money being allocated to study gender differences in healthcare [15]. However, while there have been several thorough analyses on trials, as reported in scientific journals and the Cochrane Database of Systematic Reviews, the publicly available data from registration authorities have not been assessed recently.

Therefore, the present study investigated the extent to which women have been included in clinical trials used for drug registration. As no review of data of approval dossiers was available, we performed a structured, cross-sectional study of the publicly available registration dossiers of FDA-approved and frequently prescribed drugs, and also compared these to disease prevalence between the genders.

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Furthermore, we analysed quantitative and qualitative differences in drug effect and safety between men and women in these clinical trials.

Materials and methods

A cross-sectional, structured study was performed of publicly available registration dossiers of FDA-approved drugs that are frequently prescribed on-label for the 10 most frequently occurring drug classes, as reported by the IMS health report [16]. The following drug classes were selected: antidepressants, lipid regulators, narcotic analgesics, antidiabetics, angiotensin-converting enzyme inhibitors, beta blockers, respiratory agents, antiulcerants, diuretics and antiepileptics [16]. Furthermore, we analysed compounds with high hepatic clearance or with a known gender-related difference in drug response. The selection category for each drug is specified in Table 1, while the total list of drugs used in these analyses is presented in Table S1.

Extraction of gender data

Using the FDA drug database, initial approval documents were searched for all drugs selected. These were evaluated for availability of gender data; only drugs for which information on gender data was available were included in the analyses. Data on the year of marketing approval, gender of participants by clinical phase, and qualitative subgroup analyses were extracted. Both clinical efficacy and safety data were extracted as well as pharmacokinetic data. When phase I and phase II trials were not explicitly distinguished in the FDA file, then these clinical pharmacology studies were combined.

Disease prevalence data

US disease prevalence data were collected via the Centers for Disease Control and Prevention (https://www.cdc.gov). If these data were unavailable, the sources were used as referenced in Table 1 and supplemented by drug use data. For one drug, there were no data available on either US disease prevalence or US drug use, so data on drug use in the Netherlands were used instead. Prevalence data were obtained for periods as close as possible to the year of drug marketing approval (see Table 1). The average time between approval and reported prevalence data was 3.8 years, and ranged from 0 to 12 years. Data on gender were stratified by phase of the clinical trial.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [17].

Results

Drug characteristics

An initial pool of 137 drugs (Appendix 1) was narrowed down to 46 drugs for which review data were available. From these

46, eight drugs could not be included owing to a lack of clinical phase data in the review documents. Of the 38 remaining drugs, 55% (n = 21) had been approved between 2000 and 2009, and only two drugs (5%) had been approved before the publication of the 1993 FDA guidelines on gender inclusion. Thirty-two per cent of the drugs had been approved between 1990 and 1999, and 10% of drugs during or after 2010. Most of the drugs were selected because of their inclusion in a drug class that was in the top 10 most utilized [16] while only three drugs were included because of known differences in pharmacokinetics or pharmacodynamics (Table 1). The disease states for which the drugs were intended included various indications. Diabetes was the most prevalent disease indication (21%), followed by epilepsy, depression and gastroesophageal reflux disease, each with an incidence of 13% (Table 1).

A total of 185 479 subjects participated in the drug trials reported in the retrieved registration dossiers. Of the entire population, 47% of trial participants were female, 44% were male and gender information were missing from 9%, as presented in Table 2. Thus, gender data were available for 91% of the trial subjects included in the registration dossiers. Differences in the proportions of female participation were apparent when the data were broken down into the different drug development phases (Table 2). Twenty-two per cent of the participants in phase I trials, 48% of those in phase II trials and 49% of those in phase III trials were female. Gender distribution was similar for phase I trials and combined I/II studies (25% female), and the latter category had the highest percentage (31%) of participants of unknown gender (Table 2).

All the drug trial data were compared with the disease prevalence data that were available, which were often from the same time period as the market authorization. The proportions of females in the trial populations ranged from 25% (topiramate) to 87% (milnacipran), while the prevalence of disease in women for the drugs' indication ranged from 45% for rosuvastatin to 78% for zolpidem. The difference between the proportion of females with the disease and the proportion of females in the clinical trials ranged between 0.7% and 29% for saxagliptin and topiramate, respectively (Figure 1B). Ten drugs had a greater than 20% difference between the proportion of females with the disease and the proportion of females in the clinical trials. For the majority of drugs, this percentage was similar (Figure 1).

In addition to the quantitative data retrieved, qualitative gender subgroup analyses were available for 95% of the drugs studied. For 50% of the investigated drugs, gender subgroup analyses were available with regard to efficacy. Subgroup analyses were available for both efficacy and safety for 21% of drugs, and for safety alone for 24% of drugs (Figure 2).

For 82% of the drugs for which a subgroup analysis on efficacy by gender was performed, no difference was found between men and women. Eleven per cent of the drugs were found to be more efficacious in males, and 7% were found to be more efficacious in females (Figure 3). Of the drugs that showed gender differences in efficacy, only one had a difference that was greater than 10% – palonosetron, which is indicated for chemotherapy-induced nausea and vomiting. When used for highly emetogenic chemotherapy, this drug

Table 1

Characteristics of analysed drugs and corresponding disease prevalence data. US prevalence data were retrieved from the US Centers for Disease Control and Prevention, or otherwise specified in the table

Drug	Year approved	Disease state	Prevalence data year	Reason for inclusion
Atorvastatin	1996	Hypercholesterolaemia	2000	Most utilized drug class
Celecoxib	1998	Antirheumatic	2005	Hepatically cleared
Citalopram	1998	Depression	2000	Most utilized drug class
Desvenlafaxine	2008	Depression	2010	Most utilized drug class
Dexlansoprazole	2009	GERD	1997 [32]	Most utilized drug class
Duloxetine	2004	Depression	2000	Most utilized drug class
Empagliflozin	2014	Diabetes	2012	Most utilized drug class
Eplerenone	2002	Heart failure	2000 [33]	Most utilized drug class
Escitalopram	2001	Depression	2000	Most utilized drug class
Esmolol	1986	Hypertension	1991	Most utilized drug class
Esomeprazole	2001	GERD	1997 [32]	Most utilized drug class
Exenatide-4	2005	Diabetes	2005	Most utilized drug class
Ezetimibe	2002	Hypercholesterolaemia	2000	Most utilized drug class
Formoterol	2001	Asthma	2001	Most utilized drug class
Insulin aspart	2000	Diabetes	2000	Most utilized drug class
Insulin degludec	2015	Diabetes	2012	Most utilized drug class
Irbesartan	1997	Hypertension	2001	Most utilized drug class
Lansoprazole	1995	GERD	1997 [32]	Most utilized drug class
Levetiracetam	1999	Epilepsy	1990	Most utilized drug class
Liraglutide	2010	Diabetes	2012	Most utilized drug class
Milnacipran	2009	Depression	2010	Most utilized drug class
Mometasone	2005	Asthma	2005	Most utilized drug class
Montelukast	1998	Asthma	2001	Most utilized drug class
Olanzapine	1996	Schizophrenia	2005 [34]	Most utilized drug class
Olodaterol	2014	COPD	2013	Most utilized drug class
Oxcarbazepine	2000	Epilepsy	1990	Most utilized drug class
Palonosetron	2003	Chemotherapy-induced nausea & vomiting[a]	2010 [35]	Hepatically cleared + known gender difference
Pantoprazole	2000	GERD	1997 [32]	Most utilized drug class
Pioglitazone	1999	Diabetes	2000	Most utilized drug class
Rabeprazole	1999	GERD	1997 [32]	Most utilized drug class
Rosuvastatin	2003	Hypercholesterolaemia	2005	Most utilized drug class
Rufinamide	2008	Epilepsy	2010	Most utilized drug class
Saxagliptin	2009	Diabetes	2005	Most utilized drug class
Sitagliptin	2006	Diabetes	2005	Most utilized drug class
Tiotropium	2004	COPD	2013	Most utilized drug class
Topiramate	1996	Epilepsy	1990	Most utilized drug class
Vigabatrin	2009	Epilepsy	2010	Most utilized drug class
Zolpidem	1992	Insomnia	2000 [36]	Most utilized drug class + known gender difference [37]

COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease
[a]Drug use data obtained from the Netherlands for **ondansetron** and **granisetron**

Table 2

Proportion of women in clinical studies, according to development phase

Development phase	Number of drugs	Female participation	Percentage	Unknown gender: proportion	Unknown gender: percentage
Phase I	9	788/3600	22%	798/4398	18%
Phase II	9	3477/7268	48%	987/8255	12%
Combined phase I/II	29	3024/11 881	25%	5344/17 225	31%
Phase III	38	71 049/145 296	49%	10 305 /155 601	7%
Total	38	78 338/168 045	47%	17 434 /185 479	9%
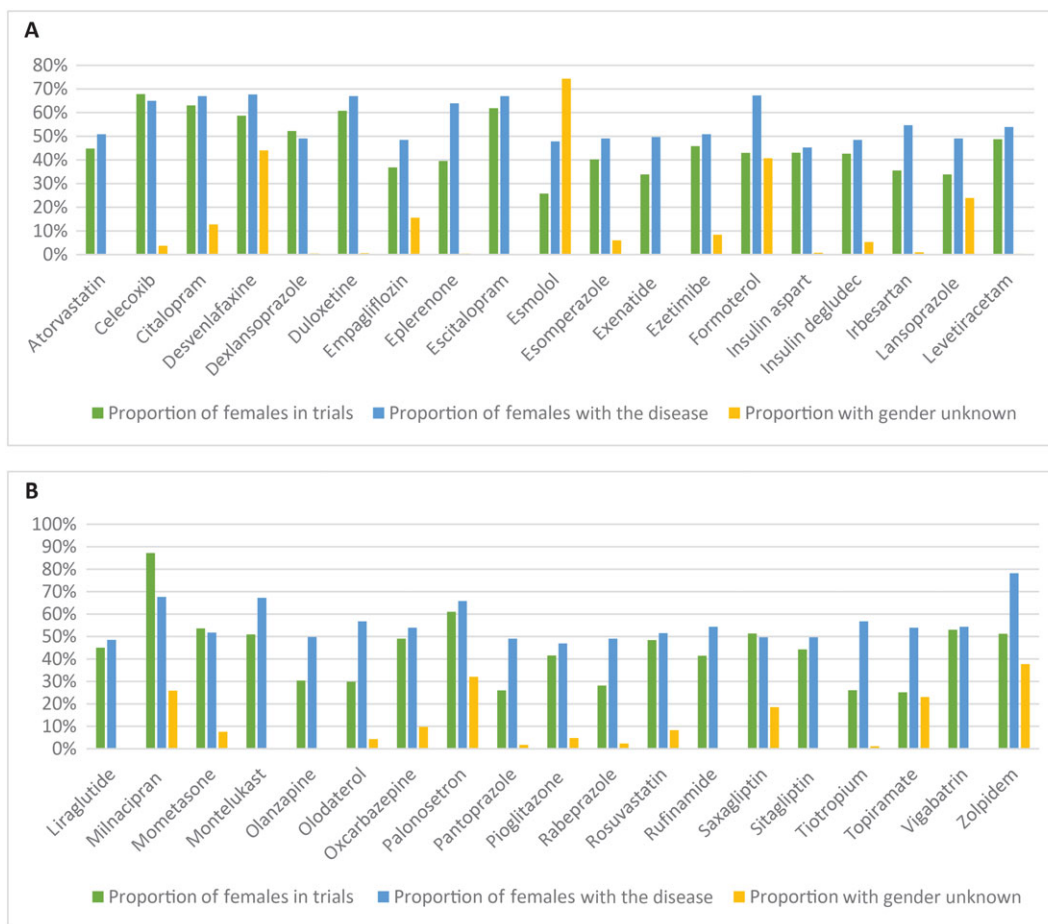
Figure 1

Bar graph representing the percentages of females participating in clinical trials (green bars) *vs*. the proportion of females with the disease, and the proportion for whom no gender was reported (yellow). The drugs are listed alphabetically, from A–L (A) and Li–Z (B)

had 90% efficacy in males and 67% efficacy in females. For moderately emetogenic chemotherapy, the efficacy in males and females were 67% and 52%, respectively.

The gender-specific safety analysis showed that for 53% of the drugs, females reported more side effects than males (Figure 4), although the nature of these side effects was generally identical and the differences were small. Only zolpidem showed a large difference in the frequency of side effects, with women reporting twice as many adverse events as men. For the other drugs, the difference in the frequency of side effects ranged from 5% to 13%, or were not reported.
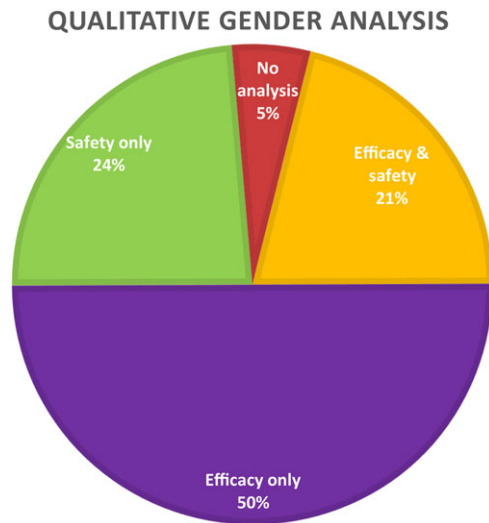
Figure 2

Pie chart representing the outcomes of the qualitative gender analysis. Subgroup analysis of the retrieved drug data was performed for efficacy (purple), safety (green), and efficacy and safety (yellow). For a small proportion, no subgroup analysis was performed (red)
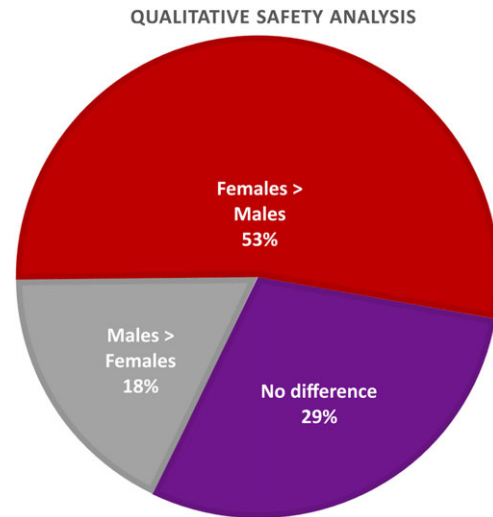

Figure 4

Pie chart representing the outcome of the qualitative safety analysis, with the purple area representing no difference between men and women, the red area representing more adverse events reported in women than in men, and the grey area representing more adverse events reported in men than in women
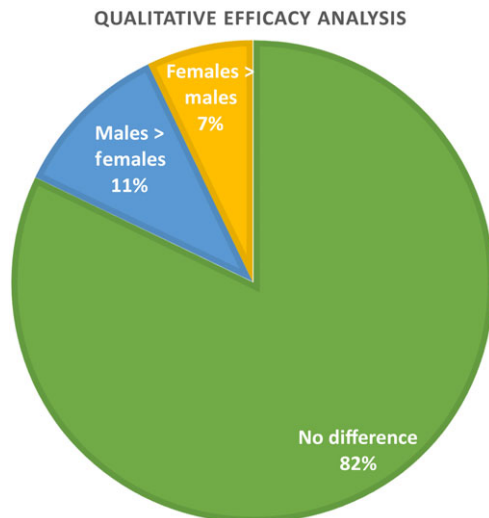

Figure 3

Pie chart representing the outcome of the qualitative efficacy analysis, with the green area representing no difference between men and women; the yellow area representing higher efficacy in women than in men; and the blue area representing higher efficacy in men than in women

Only a few drugs showed different side effect profiles between the genders. Insulin degludec showed an increased risk of cardiovascular-related events in males, with no such increase in females. Tiotropium was associated with urinary side effects only in males, with a higher risk of dry mouth, pharyngitis, and upper respiratory tract infections in females.

Discussion

Our data showed that, overall, women are studied in adequate proportions, and that some type of gender subgroup analysis is performed for most drugs that are approved. The subgroup analyses on efficacy showed that the majority of drugs are equally effective in males and females. While there was a higher proportion of females with side effects compared with males, these differences were relatively small, and likely to be of little clinical significance. It is important to realize that gender difference is one of many variables that cause variability in drug response for efficacy and/or safety in any target population. Other factors include weight, age, genotype, phenotype, ethnicity, hormonal status, fasting conditions, polymorphisms of metabolizing enzymes, receptor expression and sensitivity, co-medication interactions, co-morbidities, pregnancy status, gut microbiome status [18–22]. Many of these factors are known to induce substantially more variability than gender if they are distributed heterogeneously in the target population [21, 22]. For instance, weight is often correlated closely with drug distribution and can vary by as much as double in Western populations, thereby giving rise to substantial differences in drug response when a similar oral dose is taken, especially in obese patients [23]. Furthermore, children and the elderly are often underrepresented in registration trials, although guidelines advise that these groups are investigated [24–26]. Therefore, it is crucial for governmental bodies and funders to prioritize research based on a rational approach. Although division of the human population by gender is easy, the expected variability in response does not seem to outweigh the costs and efforts needed when demanding a more stringent approach in drug registration as indeed suggested by our review. Other sources of variability, such as body weight and genetic polymorphism

in drug metabolizing enzymes, cause substantially more clinically relevant issues and should be dealt with first in the attempt to move to personalized medicine [22, 27, 28].

To our knowledge, the present study was the first structured investigation conducted on gender differences in trial participation based on publicly available FDA registration data. Moreover, our study investigated female participation by clinical drug development phase and compared with the total proportions of females studied to gain marketing approval. Most studies chose to look at just one phase, at total numbers or at a random assortment of phase I–III studies without classifying them according to the drug approved [6, 8, 10]. Overall, a fairly even proportion of women (47%) were included in the clinical trials on the drugs included in our review. While there was a large difference in gender participation in early-phase drug development trials, with only 22% of subjects in phase I trials being female, a trend towards higher levels of female participation in later phases of these trials was observed, as also demanded by regulators, including the European Medicines Agency (EMA) [29] and the FDA [4]. Of note, phase I trials are carried out in much smaller populations than the large, later-stage clinical trials that are typically designed for efficacy and safety. In addition, the impact of these studies on the eventual use of the medication is limited. Indeed, when enough females are included in the pivotal clinical trials to detect differences in efficacy and safety between men and women, the occasional larger gap between female representation and the prevalence data is of less importance in phase I trials. Of the drugs selected, esmolol was the only one for which a large sample of women was not included in the clinical trial, and for which no gender analysis was performed. Seventy-four per cent of gender data were not reported for this drug. However, for a drug that has been on the market for over three decades and for which close monitoring during (in-hospital) use is mandatory, it is unlikely that further research will result in new gender-specific recommendations for use.

A limitation of our study was that it was based on a relatively small sample of drugs (38), so selection bias could not be excluded. However, these 38 drugs represented a sample of frequently prescribed compounds of the most utilized therapeutic classes in the US, and 185 479 trial participants were included in our analyses. Although it could be argued that the situation would be completely different for drugs that are used to a lesser extent, this is at present speculative. Further research could include a comparison between registration data and actual prescribing patterns from a healthcare database for less frequently used drugs, to address this potential difference. A similar analysis could and should be performed for more, or all, drugs available, before concluding that females are under-represented. Such an exercise would be far cheaper and quicker than spending public money to solve an unsubstantiated research question. It is also remarkable that various FDA reports had missing information; as noted, 9% of gender data overall were missing. This may have had an impact on our findings, but would have been unlikely to alter the overall conclusion. In line with other recent studies, we found that subgroup analysis of gender is not fully reported, with the majority (79%) of reports lacking either safety or efficacy analysis (Figure 2) [30, 31]. In addition, there is no way to ascertain whether all data submitted to the FDA are available in the online published review. Some information had been redacted because of confidentiality considerations. While gender data were not always included in the published FDA data online, it is unclear whether the FDA would have had access to these originally. In general, the issue of missing data in public reports should not be considered synonymous with market authorization based on incomplete data submission. Obviously, it would have been better if these data, when available, had been included in documents that are in the public domain. We suggest that publication of the gender composition of all clinical trials of new drugs, regardless of the phase of development, should be mandatory.

In conclusion, we found no evidence of any systematic under-representation of women. This conclusion is in line with that of the FDA, EMA and a recent Cochrane meta-analysis [8]. Such research, and the present analysis, may help in future decision making about performing drug research focused on gender differences for new and existing compounds.

Competing Interests

There are no competing interests to declare.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

http://onlinelibrary.wiley.com/doi/10.1111/bcp.13497/suppinfo

Table S1 Initial drug list