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Brief Communications

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From clinical trials to clinical practice: How long are drugs tested and then used by patients?

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ABSTRACT

Objective: Evidence is scarce regarding the safety of long-term drug use, especially for drugs treating chronic diseases. To bridge this knowledge gap, this research investigated the differences in drug exposure between clinical trials and clinical practice.

Materials and Methods: We extracted drug follow-up times from clinical trials in ClinicalTrials.gov and compared the difference between clinical trials and real-world usage data for 914 drugs taken by 96 645 927 patients.

Results: A total of 17.5% of drugs had longer median exposure in practice than in trials, 6% of patients had extended exposure to at least 1 drug, and drugs treating nervous system disorders and cardiovascular diseases were the most common among drugs with high rates of extended exposure.

Conclusions: For most of patients, the drug use length is shorter than the tested length in clinical trials. Still, a remarkable number of patients experienced extended drug exposure, particularly for drugs treating nervous system disorders or cardiovascular disorders.

Key words: randomized controlled trials, evidence-based medicine, prescription drug overuse, follow-up studies, validation study

INTRODUCTION

Randomized controlled trials (RCTs) are well accepted as the gold standard for generating evidence about the safety and efficacy of medical products. However, this evidence can lack generalizability to real-world clinical practice, often owing to insufficient statistical power or lack of applicability among the real-world use populations.[1–3] Moreover, there is insufficient evidence about the safety of long-term drug use beyond the duration of RCTs. New adverse drug reactions and effects of prolonged drug use can be detected in clinical practice,[4–8] in which patients may take pharmacologic treatments for extended periods of time, especially for chronic disease management.[9–11] This study initially investigates how the duration of RCTs compares with the observed length of drug exposure in clinical practice at scale by leveraging public clinical trial summaries and real-world drug use data for a large population .

METHODS

We employed 2 data sources, clinical trial summaries from ClinicalTrials.gov and large-scale observational clinical claims data from the Truven MarketScan Commercial Claims and Encounters database.[12] Our methodology framework is illustrated in Figure 1. We

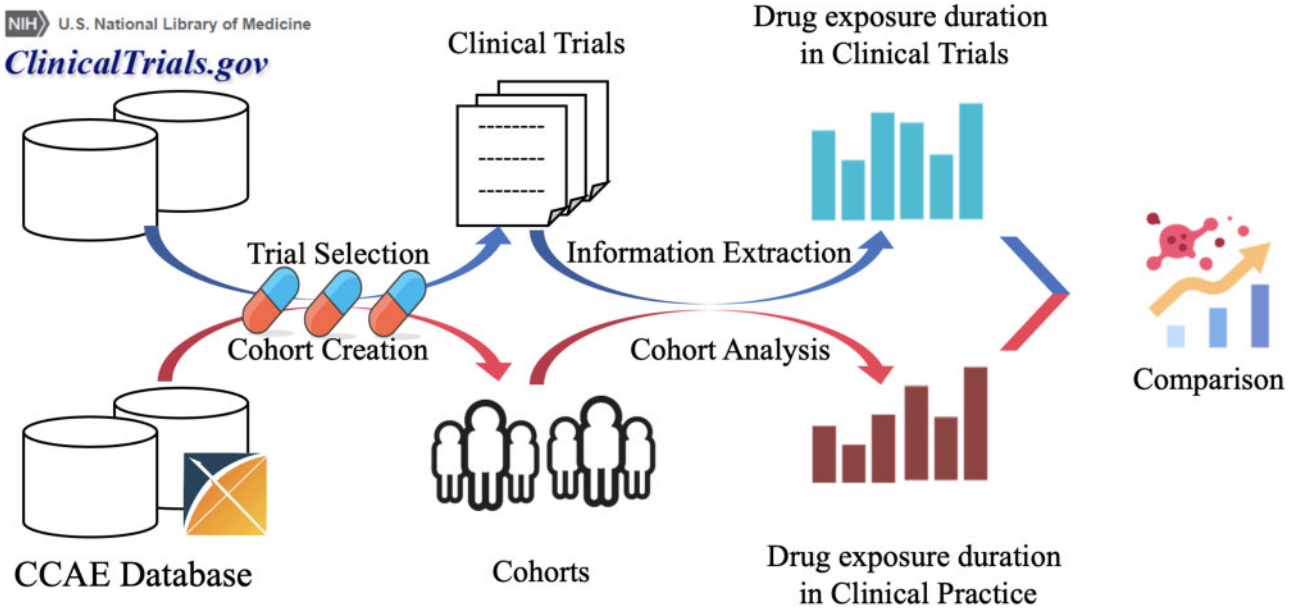

Figure 1. Comparison between drug exposure duration in trials and clinical practice. CCAE: Commercial Claims and Encounters.

identified all Phase 3 interventional trials in ClinicalTrials.gov as of August 2017. All conditions and interventions were extracted and mapped to Observational Medical Outcomes Partnership CDMv5.1 standard concepts.[13] Follow-up times for each arm were extracted with a heuristic-based method and normalized by SUTime.[14] We created cohorts against the outpatient pharmacy dispensing claims data in the Commercial Claims and Encounters database for each drug ingredient, with a requirement of minimally 1 year of continuous observation of the patients before and after initial drug exposure. We calculated the exposure duration by aggregating successive dispensing records and assigning discontinuation if 30 days passed since the last dispensing date plus supply duration without another dispensation. When a patient was clinically exposed to a drug longer than the drug's maximum RCT follow-up length, we counted it as an instance of "extended exposure." We estimated the proportion of patients taking each drug that had exposure lengths greater than the maximum RCT follow-up length ("extended exposure"). Results were summarized across the drug portfolios and ingredients, with the latter being grouped into the Anatomical Therapeutic Chemical classification system[15] for comparison across the therapeutic areas. We also compared the changes of trial numbers and patient counts over drug exposure duration.

RESULTS

A total of 9135 phase 3 trials were extracted from ClinicalTrials.gov, covering 1670 drugs that correspond to 1220 drug ingredients. From a commercial claims database, 914 of these drug ingredients were observed in clinical practice, and 96 645 927 patients had exposure to at least 1 of them. A total of 6% of patients had extended exposure to at least 1 drug. A total of 17.5% (n = 160 of 914) of drugs had longer median clinical exposure times than median RCT follow-up times. We subsequently selected the more thoroughly tested drugs by including drugs tested in more than 5 trials and in which the 90th percentile of the drug's trials had more than 90 days follow-up time, yielding 478 drugs. Among these drugs, 67.8% (n = 324 of 478) of them had at least 1 patient with an extended exposure, and 9.0% (n = 43 of 478) had more than 10% of patients with extended exposures. For these 43 drugs, Table 1 shows the number of RCTs, maximum RCT follow-up duration, proportion of patients with extended drug exposure, and Anatomical Therapeutic Chemical classification.[15] Most of these drugs act on the nervous system (n = 18 of 43, 41.9%) or cardiovascular system (n = 9 of 43, 20.9%). The drugs with the highest percentages of patients with extended exposures were treprostinil (55.2%), dextroamphetamine (46.9%), and carvedilol (35.8%). Dextroamphetamine, a drug used by 530 448 patients in the claims database, was studied in 6 RCTs with a maximum follow-up of only 98 days, whereas the median and 90th percentile clinical exposure times were 88 and 588 days, respectively. Duloxetine was the most frequently tested drug (in 43 trials), followed by buprenorphine (41 trials) and citalopram (37 trials). Duloxetine was used by 549 315 patients, 12% of whom had drug exposures greater than its maximum follow-up length of 602 days. Etravirine had the longest RCT follow-up length (1260 days), yet 10.9% (n = 156 of 1432) of patients taking etravirine had extended exposures.

Figure 2 compares the RCT follow-up vs observed clinical drug exposure durations of 4 commonly used drugs: citalopram (Figure 2A), metformin (Figure 2B), warfarin (Figure 2C), and simvastatin (Figure 2D). The cumulative distributions of RCT follow-up time (orange) and clinical exposure time (green) of each drug are plotted. The figures illustrate how the percentage of trials and patient cohort size change over drug exposure time. For metformin, warfarin, and simvastatin, the RCT distribution curves are similar to or exceed the observational exposure curves. For example, 11.3% of patients had an exposure to metformin for 24 months, while 7.3% of metformin-related trials tested for the same length of time. Only a very small portion of patients had longer clinical exposures than the longest follow-up times in these clinical trials. For instance, the longest warfarin trial (NCT00041938) in our dataset had a follow-up of 72 months, while only 0.2% of patients were exposed to warfarin for more than that. For citalopram, clinical exposure in patients generally exceeded RCT follow-up. A total of 61.0% and 18.4% of patients were exposed to citalopram for at least 2 and 12

Table 1. Forty-three drugs with over 10% of patients with extended exposure

Ingredient	Number of RCTs	Max RCT Length (days)	Patients With Extended Exposure	ATC first level
Treprostinil	6	112	259/469 (55.2%)	B
Dextroamphetamine	6	98	248 803/530 448 (46.9%)	N
Carvedilol	14	360	900 06/251 472 (35.8%)	C
Amphetamine	11	168	177 150/519 072 (34.1%)	N
Vilazodone	7	180	15 362/46 017 (33.4%)	N
Nebivolol	6	371	44 077/142 588 (30.9%)	C
Buprenorphine	41	365	13 510/44 846 (30.1%)	N
Sodium oxybate	8	365	811/2890 (28.1%)	S
Donepezil	19	392	4674/18 516 (25.2%)	N
Cabergoline	6	210	4482/18 030 (24.9%)	N
Venlafaxine	16	365	140 444/565 191 (24.8%)	N
Isosorbide	12	365	20 892/95 677 (21.8%)	C
Colesevelam	7	168	22 621/104 676 (21.6%)	C
Lisdexamfetamine	18	371	58 926/298 487 (19.7%)	N
Mirabegron	14	390	3055/16 331 (18.7%)	G
C1 esterase inhibitor	6	730	27/146 (18.5%)	B
Citalopram	37	365	172 022/948 463 (18.1%)	N
Enfuvirtide	6	672	57/319 (17.9%)	J
Maraviroc	13	1008	90/518 (17.4%)	J
Naloxone	18	245	15 512/90 005 (17.2%)	V
Brexpiprazole	18	364	311/1844 (16.9%)	N
Pitavastatin	11	420	4450/27 184 (16.4%)	C
Paroxetine	24	364	21 329/136 957 (15.6%)	N
Leflunomide	8	497	3 400/23 416 (14.5%)	L
Armodafinil	25	360	5714/41 386 (13.8%)	N
Bosentan	13	1204.5	134/975 (13.7%)	C
Olodaterol	25	392	148/1091 (13.6%)	R
Rasagiline	11	912.5	634/4731 (13.4%)	N
Glatiramer	11	1095	1778/13 355 (13.3%)	L
Glipizide	12	728	28 275/216 827 (13%)	A
Nifedipine	6	540	19 905/153 501 (13%)	C
Modafinil	25	360	11 061/87 279 (12.7%)	N
Calcitriol	17	360	6547/52 345 (12.5%)	A
Lithium carbonate	18	510	8589/70 516 (12.2%)	N
Duloxetine	43	602	66 021/549 315 (12%)	N
Latanoprost	22	360	12 022/101 063 (11.9%)	S
Clonidine	18	365	35 685/302 279 (11.8%)	N
Propranolol	10	365	37 359/318 422 (11.7%)	C
Tolterodine	15	390	17 788/153 522 (11.6%)	G
Furosemide	9	364	70 512/624 964 (11.3%)	C
Sevelamer	14	364	1482/13 234 (11.2%)	V
Etravirine	8	1260	156/1432 (10.9%)	J
Riluzole	7	720	147/1407 (10.4%)	N

Values are n or n/n (%).

The ATC classification system abbreviations are the following: A (alimentary tract and metabolism), B (blood and blood forming organs), C (cardiovascular system), G (genitourinary system and sex hormones), J (antiinfectives for systemic use), L (antineoplastic and immunomodulating agents), N (nervous system), R (respiratory system), S (sensory organs), and V (various).

ATC: Anatomical Therapeutic Chemical; RCT: randomized controlled trial.

months, respectively, whereas only 45.9% of citalopram trials followed-up for 2 or more months, and no trials followed up for more than 12 months.

DISCUSSION

Drugs treating nervous system disorders were notable among the drugs with high frequencies of extended exposures, accounting for 41.9% (n = 18 of 43) of the drugs that each have over 10% of patients with extended exposure in Table 1. In particular, antidepressants, including duloxetine, venlafaxine, and citalopram, were not only tested in many RCTs but also used by a large number of patients in clinical practice when compared with other drugs. The maximum RCT follow-up durations of duloxetine, venlafaxine, and citalopram are more than 1 year, which is longer than the usual initial treatment duration for unipolar major depression.[11,16] Still, a large proportion of patients were exposed to these drugs with a duration longer than the maximum RCT follow-up duration, eg, 18.4% of patients were exposed to citalopram for more than 1 year. Long-term exposures of antidepressants and antipsychotics were also observed in other cohort studies as well as in primary care databases outside of the United States.[17,18] In order to better perform

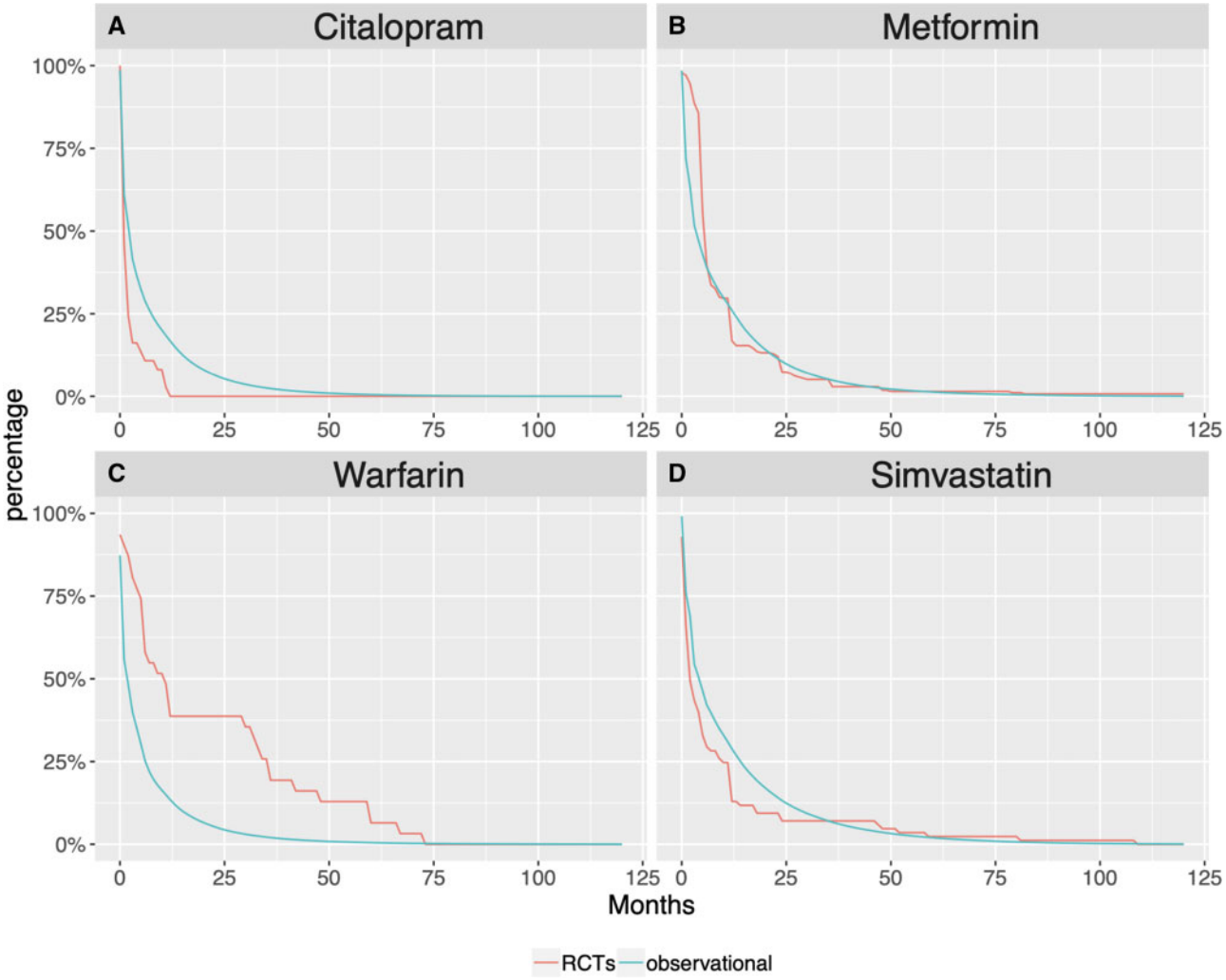

Figure 2. The trials and observational data curves indicating the lengths of trial follow-up time and clinical exposure time of 4 selected drugs: (A) citalopram, (B) metformin, (C) warfarin, and (D) simvastatin. The x-axis stands for the exposure duration with the unit being a month, and we used a standard 30-day period for all months. The y-axis stands for the percentage of randomized controlled trials (RCTs) (orange line) and the percentage of exposed patients (green line), respectively.

postmarketing surveillance for these drugs with prolonged exposure in real-world patients, postauthorization safety studies[19] have been established in Europe. Additionally, pragmatic trials could also be a potentially useful method to study the benefits and safety of extended drug exposure in real-world uses.[20]

Patients taking a drug for longer than the follow-up time in clinical trials are at risk of unknown potential long-term adverse events and side effects.[6,9] The results from this study promise to inform future clinical practice and clinical research. Clinicians and patients can review the results from this research to better understand the thoroughness of investigation in clinical trials for those drugs with extended exposure in real-world uses. Trial designers can query how many patients have long-term exposure for specific drugs and hence make informed trial design decisions to balance cost-effectiveness and safety to avoid unsafe real-world extended drug exposure.

One year was the most common maximum follow-up duration in RCTs of 43 thoroughly tested sets of drugs. Considering the cost and human effort required to conduct RCTs, it is not trivial to conduct RCTs with longer follow-up durations. Furthermore, when lengthening study durations, the possibility of increasing participant drop-out rates over the duration of follow-up and the emergence of novel treatment options also complicate matters. However, our study revealed that a substantial number of patients are subject to long-term exposure of drugs. For drugs that are commonly used for longer periods, such as those treating nervous system disorders or cardiovascular diseases, evidence obtained from RCTs may be supplemented by evidence from well-designed observational studies with long-term follow-up periods. It would be necessary to conduct an observational study that encompasses multiple sites to include enough patients with long-term exposure. Cumulative or latent risks that are associated with long-term exposure of drugs could be captured with sufficient follow-up in observational studies.

There are several limitations to this study. The data available in ClinicalTrials.gov are not sufficient for detailed characterization and analysis of drug exposure durations. For example, information about the total enrollment count is available, but enrollment count for each trial arm is not. Furthermore, marketing authorization holders are sometimes required in their risk management plan to contemplate phase 4 studies or observational ones to make longer follow-ups to fulfil the requirements. We may have missed such information for newly devel-

oped drugs. Because drug exposure duration in RCTs was not broadly available, we used follow-up time as an upper-limit proxy for drug exposure duration. Future enhancements to ClinicalTrials.gov may enable richer analyses. Moreover, in the real-world data analysis, drug exposures with different formulations and strengths were ignored and aggregated at the ingredient level. When inferring clinical drug exposure durations, we estimated continuous exposure windows for each patient, which may underestimate the total drug exposure when patients temporarily discontinued use of a drug or when their medication was not captured by the claims database.

CONCLUSIONS

This study contributes one of the earliest findings about the drug exposure length differences between clinical trials and clinical practice. A remarkable number of patients experience extended drug exposure, particularly for drugs treating nervous system disorders or cardiovascular disorders. Future studies are warranted to investigate if drugs in use longer than in the trials actually have different safety profiles from those who do not have extended use in practice.

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AUTHOR CONTRIBUTIONS

CY, PBR, and CW conceived of the study. CY and PBR conducted data processing and analysis, supervised by CW. CY drafted the manuscript, which was edited and approved by all authors.

DATA AVAILABILITY STATEMENT

The data is publicly available without restriction at our GitHub repository: https://github.com/WengLab-InformaticsResearch/Generalizability_of_RCT_Follow_Up_Time/tree/main/data

CODE AVAILABILITY STATEMENT

The code that was used to preprocess and analyze the data is available from the corresponding author upon request.

CONFLICT OF INTEREST STATEMENT

The autors declare no competing interests.

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