Received: 3 February 2022 | Revised: 17 July 2022 | Accepted: 3 August 2022

DOI: 10.1111/bcp.15486

ORIGINAL ARTICLE

The association of chiral characteristic with drug withdrawal due to safety: A comparative analysis

Volkan Aydin[1] | Ayfer Bahar[2] | Caner Vizdiklar[2] | Ahmet Akici[2]

[1]Department of Medical Pharmacology, International School of Medicine, Istanbul Medipol University, Istanbul, Turkey

[2]Department of Medical Pharmacology, School of Medicine, Marmara University, Istanbul, Turkey

Correspondence
Prof. Ahmet Akici, MD, Department of Medical Pharmacology, Marmara University School of Medicine, Maltepe 34854, Istanbul, Turkey.
Email: aakici@marmara.edu.tr and ahakici@gmail.com

Aims: Chirality of drugs might be associated with safety issues through pharmacokinetic or pharmacodynamic variations, interactions, or direct toxicological responses. We aimed to compare chiral status of the available drugs to that of drugs withdrawn due to adverse drug reactions (ADRs).

Methods: We searched the literature regarding withdrawn drugs due to safety-related issues ($n = 391$) to compare them with all available small-molecule drugs ($n = 1633$). We examined their chiral status and assigned as achiral compound, chiral mixture or pure enantiomer. We compared the mean survival (i.e., nonwithdrawal) time and withdrawal rates of drugs by their chirality, with further stratification by the launch year, ATC-1 (Anatomical Therapeutic Chemical) level and ADR.

Results: We identified higher withdrawal rate in achiral drugs (hazard ratio 2.1, 95% CI: 1.6–2.7) and chiral mixtures (hazard ratio 2.6, 95% CI: 1.9–3.5) compared to that in pure enantiomers. Pure enantiomers had the longest mean survival time (62.4 ± 0.8 years), followed by achiral drugs (55.4 ± 0.9 years, $P < .01$) and chiral mixtures (52.4 ± 1.4 years, $P < .01$). Pure enantiomers had higher survival rates than chiral mixtures if launched before 1941 ($P = .02$), in 1961–1980 ($P < .001$) or 1981–2000 ($P < .001$). Pure enantiomers had lower withdrawal rate (18.2%) *vs*. chiral mixtures (35.1%, $P = .02$) in nervous system drugs. Pure enantiomers had lower withdrawal rate than chiral mixtures in hepatotoxic ($P < .01$) and cardiovascular ADRs ($P < .01$).

Conclusion: Our study showed lower likelihood of withdrawal for pure enantiomers compared to that in chiral mixtures and achiral drugs, which was more remarkable for those launched in certain time periods and several ADRs, including hepatotoxicity and cardiovascular toxicity.

KEYWORDS
drug regulation, pharmacoepidemiology, pharmacovigilance, pure enantiomer, stereoisomerism

1 | INTRODUCTION

Chirality is an important geometric characteristic of the objects within biological systems including amino acids, carbohydrates and lipids as well as drugs.[1] In the latter, chirality might be associated with safety issues through pharmacokinetic or pharmacodynamic variations, drug interactions or direct toxicological responses.[2] Chiral drugs consist of racemic mixtures, nonracemic mixtures or pure enantiomers.[3] Unlike achiral drugs with no chiral centre, this stereoisomeric chemistry allows the opportunity to manipulate their composition or molecular chirality to enhance efficacy and/or overcome tolerability problems.[4] A typical example of improving clinical efficacy could be given as selective H1-receptor antagonist, cetirizine, whose R-enantiomer levocetirizine has 30-fold higher binding affinity and lower renal

clearance compared to its parent racemic mixture.[5,6] By contrast, thalidomide represents a well-known dramatic example of drug-induced toxicity and subsequent withdrawal, with R-enantiomer responsible for the intended sedative effect and S-enantiomer for the tragic phocomelia.[7,8]

Use of pure enantiomers offers advantages including dose reduction, simplification of dose–response relationship, diminution of inter-individual variability and toxicity from inactive enantiomers.[9] In fact, regulatory drug authorities encourage such chemical designations for novel drug development.[10] In addition, some racemic mixtures have undergone chiral switch, where their pure enantiomers were launched with same/similar indication.[11] These have led to increased share of pure enantiomers worldwide although many racemic and nonracemic mixtures are still present.[2] While several clinical efficacy and/or safety benefits have been attributed to pure enantiomer drugs, there has been no systematic analysis that investigated these aspects with respect to chirality. In this study, we aimed to compare chiral status of the available drugs to that of drugs withdrawn due to adverse events.

What is already known about this subject

- Chiral status of drugs is postulated to be among the factors that influence drug safety through pharmacokinetic/pharmacodynamic changes, toxicities or drug interactions.
- There has not been any systematic analysis that investigated safety issues/benefits attributed to chiral status.

What this study adds

- Pure enantiomers were less likely to be withdrawn than chiral mixtures and achiral drugs.
- The survival advantage of pure enantiomers was most pronounced for those launched before 1941 and between 1961 and 2000.
- Assessment of withdrawal-related adverse drug reactions revealed the tendency of chiral mixtures towards hepatotoxicity, cardiovascular, abuse-related and dermatological adverse drug reactions.

2 | METHODS

In this pharmacoepidemiological study, we collected and analysed retrospective descriptive drug safety data. Prior to data collection, ethical approval was obtained from the Ethics Committee for Non-Interventional Clinical Studies of Marmara University Institute of Health Sciences (approval number: 16.11.2020–91).

We examined the chemical structures regarding chirality status of the drugs that were withdrawn from the market around the world due to adverse effects and compared to those still available on the worldwide market. Drugs withdrawn between 1950 and 2020 in the world due to safety-related issues were identified via literature search. Those withdrawn between 1950 and 2014 were obtained from a systematic review conducted by Onakpoya *et al*., including a total of 462 drugs/products.[12] Drugs/medicinal products that contain inorganic compounds (as classified in IUPHAR/BPS Guide to PHARMACOLOGY),[13] proteins, vaccines, polymers, human tissue extracts, herbal and cell-based preparations as active substances, medical devices, drug groups not identifying specific active substances, and combinations of 2 or more active substances that show different chiral status from each other were excluded from the study. The remaining 385 drugs, i.e., those that comprise single active substance ($n = 379$) and the combinations of active substances showing similar chiral characteristics ($n = 6$), were included. Using a methodology similar to the aforementioned review, literature search was conducted for drugs withdrawn between 2015 and 2020, which resulted in 6 drugs meeting those criteria (Table S1). Thus, a total of 391 drugs/medicinal products were included in the study as withdrawn drugs. To identify the drugs available on the market, drugs assigned to the Anatomical Therapeutic Chemical (ATC) classification were examined. ATC is a classification system created by the World Health Organization in which the active substances are classified according to target organ/system, therapeutic, pharmacological and chemical properties.[14] The complete list included a total of 4441 unique entries at the fifth level (ATC-5), which corresponds to the chemical substances.[14] After applying the exclusion criteria determined for the selection of withdrawn drugs, we proceeded to obtain approval dates of the remaining 2489 drugs. Approval dates were identified via the NCATS Inxight Drugs database of the US National Institute of Health,[15] or, if not available, the DrugBank Online database.[16] Entries without available approval/first marketing dates and those launched/approved after 2020 were excluded, and the remaining 1633 drugs/medicinal products were included in the study as survived (i.e., nonwithdrawn) drugs. Chiral characteristics and distribution of those drugs at ATC-1 level, as well as the distribution of their duration on the market, and if withdrawn, adverse drug reactions (ADRs) leading to their withdrawal were examined.

Chirality status of the drugs was identified via information on the NCATS Inxight Drugs database.[15] For those that are not available on that database, chirality status was determined after literature search. According to chiral characteristics, the drugs were assigned into 1 of 3 categories: *achiral*, *chiral mixture* or *pure enantiomer*. For the analyses regarding temporal aspects, the duration (period from introduction to the calendar year of 2020) of the drugs on the market and if withdrawn, the time to withdrawal (TtW) were examined. The index year was set as 1950 for the drugs launched before that time to compensate for the lack of well-established drug regulations that could put such old medications at risk for withdrawal. Accordingly, mean survival time of the drugs and median TtWs of the withdrawn ones by

chiral status were determined and compared. Also, the drugs were evaluated and compared by their year of launch categorically in 5 distinct periods as before 1941, 1941–1960, 1961–1980, 1981–2000 or after 2000.

Chiral distribution of the withdrawn drugs was also evaluated and compared at ATC-1 level. Before that, we re-classified drugs with multiple ATC codes or without any code by adding them to the most appropriate ATC class according to the indication led to withdrawal, whenever possible. Those drugs were evaluated and compared as achiral drugs, chiral mixtures and pure enantiomers to analyse in detail.

ADRs leading to withdrawal of drugs were evaluated in 20 subgroups (i.e., cardiovascular, genitourinary, gastrointestinal, respiratory, neurological, haematological, dermatological, immunological, psychiatric, endocrine, ophthalmic, musculoskeletal and other ADRs, along with hepatotoxicity, nephrotoxicity, genotoxicity, drug abuse, carcinogenicity, teratogenicity and death). These were distributed and compared by the chirality status (achiral/chiral mixture/pure enantiomer) of the related drugs. Moreover, the median TtWs of the most common ADRs leading to withdrawal (n ≥ 30) were determined and compared by chiral status.

2.1 | Statistical analysis

All data were analysed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 5.0 for Windows (GraphPad Software, San Diego, CA, USA) software. Analysed data were expressed as numbers and percentages or median with interquartile range. Frequency analysis was used for statistical evaluation and categorical variables were compared using χ^2 and Fisher's exact tests, where appropriate. Survival analysis was conducted using Kaplan–Meier method and Cox proportional hazards model. Kaplan–Meier analysis defined mean survival time ± standard error of mean, and log-rank test was used for related comparisons. Hazard ratio (HR) with a 95% confidence interval (CI) was calculated by univariate Cox regression analysis with pure enantiomer selected as reference category. For continuous variables, normality of distribution was evaluated by D'Agostino-Pearson or, if not applicable, Shapiro–Wilk analyses. Normally distributed data were compared using 1-way analysis of variance (ANOVA) test with Tukey's posthoc test, whereas Kruskal–Wallis test was used with Dunn's posthoc test when normal distribution was not applicable. Statistical significance was inferred by an overall 5% of Type-I error level.

3 | RESULTS

3.1 | Chirality status of withdrawn and survived drugs

A total of 391 withdrawn drugs were identified, of which 52.9% ($n = 207$) were achiral, 27.9% ($n = 109$) were chiral mixtures and 19.2% ($n = 75$) were pure enantiomers. Of the 1633 survived (i.e., nonwithdrawn) drugs, 42.4% ($n = 693$) were achiral, 16.1% ($n = 264$) were chiral mixtures and 41.5% ($n = 676$) were pure enantiomers. The rate of withdrawal was lower in pure enantiomers (10.0%) than that in achiral drugs (23.0%) and chiral mixtures (29.2%; $P < .001$, Table 1). Cox regression showed significantly increased rate of withdrawal in achiral drugs (HR 2.1, 95% CI: 1.6–2.7, $P < .001$) and chiral mixtures (HR 2.6, 95% CI: 1.9–3.5, $P < .001$) compared to that in pure enantiomers.

3.2 | Chirality status by temporal patterns

Pure enantiomers were estimated to have the longest mean survival time (62.4 ± 0.8 years), followed by achiral drugs (55.4 ± 0.9 years) and chiral mixtures (52.4 ± 1.4 years; $P < .01$ for each pairwise comparison, Figure 1). Pure enantiomers had significantly higher survival rates than chiral mixtures if launched before 1941 ($P = .02$), in 1961–1980 ($P < .001$) and 1981–2000 ($P < .001$). In contrast to the total, no difference was observed in survival rates of achiral drugs and chiral mixtures in any of the examined periods ($P > .05$; Figure 2). The median TtW of withdrawn drugs were 17 (interquartile range [IQR]: 6–29) years, with no difference between achiral drugs (median: 15, IQR: 6–28 years), chiral mixtures (median: 15, IQR: 5–29 years) and pure enantiomers (median: 20, IQR: 8–29 years; $P > .05$).

3.3 | Chirality status by ATC classification

In nervous system drugs, which were the largest fraction of both withdrawn (26.3%) and survived (15.7%) agents, withdrawal rate of pure enantiomers was lower (18.2%) than that of chiral mixtures (35.1%, $P = .02$). In addition, pure enantiomers had significantly lower withdrawal rates *vs.* achiral drugs and chiral mixtures in alimentary tract/metabolism drugs ($P < .01$ for each), systemic anti-infectives ($P < .01$ for each) and musculoskeletal system drugs ($P = .02$ for each; Table 2).

TABLE 1 Chiral distribution of the evaluated survived (nonwithdrawn) and withdrawn drugs

	Achiral		Chiral mixture		Pure enantiomer		Total		
Status	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***P*-value**
Survived	693	77.0	264	70.8	676	90.0	1633	80.7	<.001*
Withdrawn	207	23.0	109	29.2	75	10.0	391	19.3	
Total	900	100.0	373	100.0	751	100.0	2024	100.0	

*$P < .001$ for pure enantiomers *vs.* each of achiral drugs and chiral mixtures and $P = .02$ for achiral drugs *vs.* chiral mixtures.

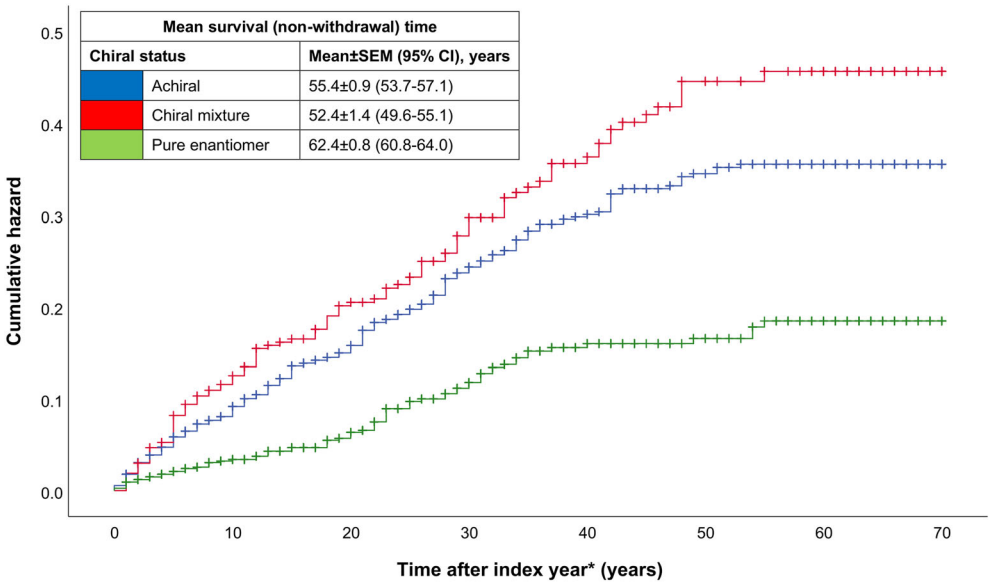

FIGURE 1 Cumulative hazard plots of the drugs after index year by their chiral status. *Index time, which was determined as 1950, was chosen as a starting point for the survived old medications that were approved/launched before that time.

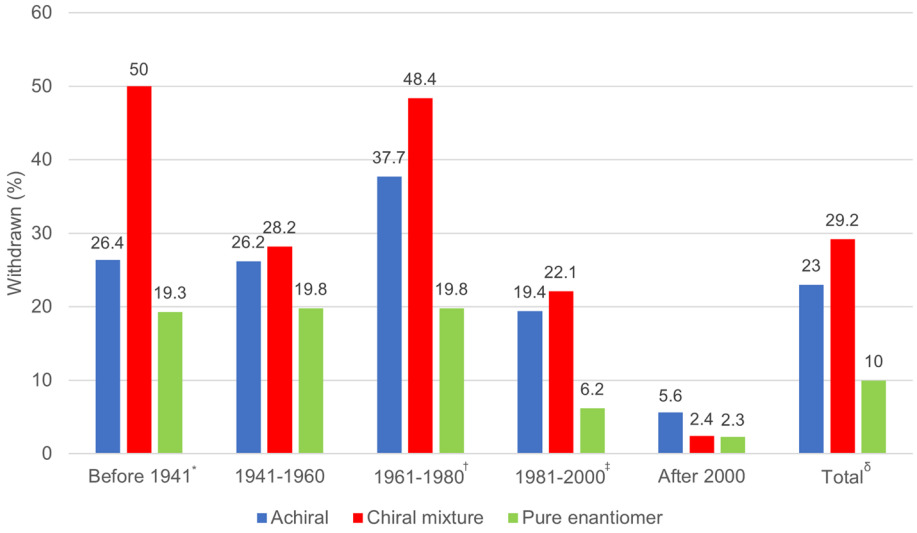

FIGURE 2 Chiral distribution of the share of withdrawn drugs by their years of launch. *$P = .02$ for pure enantiomer *vs.* chiral mixtures; †$P < .001$ for pure enantiomer *vs.* chiral mixtures and $P = .001$ *vs.* achiral drugs; ‡$P < .001$ for pure enantiomer *vs.* each of achiral drugs and chiral mixtures; §$P < .001$ for pure enantiomer *vs.* each of achiral drugs and chiral mixtures and $P < .01$ for achiral drugs *vs.* chiral mixtures.

3.4 | Chirality status by adverse drug reactions

Aside from neurological and immunological ADRs, pure enantiomer drugs were less commonly withdrawn in all ADR classes. Pure enantiomers had lower withdrawal rates compared to achiral drugs and chiral mixtures in hepatotoxicity and dermatological ADRs ($P < .01$ for both). Chiral mixtures had higher withdrawal rates than the other 2 chiral classes in cardiovascular ADRs and drug abuse ($P < .01$ for both; Table 3). The difference in TtW by type of ADR was limited to achiral drugs withdrawn due to dermatological ADRs, which had longer median TtW compared to that in chiral mixtures ($P = .02$; Table 4).

4 | DISCUSSION

We examined chirality of the drugs withdrawn from the market over the last 70 years to uncover the potential reflections of such characteristic on major safety issues that outweigh its intended benefits. We observed that pure enantiomers had a substantial survival advantage over chiral mixtures and achiral drugs, which was more remarkable in several drug groups at ATC-1 level and for those launched in certain time periods. In addition, assessment of ADRs by chiral category pointed out the tendency of chiral mixtures towards hepatotoxicity, cardiovascular, abuse-related and dermatological ADRs.

Drugs with a chiral characteristic, either in the form of racemic/nonracemic mixtures or pure enantiomers, were reported to constitute more than half (56%) of the drugs used.[17] This figure appeared to show modest increments in favour of chiral drugs, as the annual new worldwide approval rates of chiral drugs were reported to range between 50 and 76%.[18] In our study, 57.6% of the available—or survived—drugs were of chiral type with a 2.5-fold predominance of pure enantiomers over chiral mixtures. Pure enantiomer drugs may offer advantage of less complex pharmacological profile with a

TABLE 2 Comparison of chirality of the survived (nonwithdrawn) *vs*. withdrawn drugs at ATC-1 level

		Achiral		Chiral mixture		Pure enantiomer		
ATC-1	**Status**	**n**	**%**	**n**	**%**	**n**	**%**	***P*-value**
A, alimentary tract & metabolism	Survived	69	71.1	27	61.4	98	86.7	**<.001**[*]
	Withdrawn	28	28.9	17	38.6	15	13.3	
B, blood & blood forming organs	Survived	37	97.4	4	10.0	24	92.3	.57
	Withdrawn	1	2.6	0	.0	2	7.7	
C, cardiovascular system	Survived	65	80.2	59	75.6	62	86.1	.27
	Withdrawn	16	19.8	19	24.4	10	13.9	
D, dermatological	Survived	68	86.1	13	10.0	44	91.7	.26
	Withdrawn	11	13.9	0	.0	4	8.3	
G, genitourinary system & sex hormones	Survived	14	66.7	11	84.6	47	87.0	.12
	Withdrawn	7	33.3	2	15.4	7	13.0	
H, systemic hormonal preparations	Survived	2	100.0	0	.0	20	100.0	1.0
	Withdrawn	0	0.0	0	.0	0	0.0	
J, anti-infectives for systemic use	Survived	38	70.4	8	57.1	154	95.1	**<.001**[*]
	Withdrawn	16	29.6	6	42.9	8	4.9	
L, antineoplastic & immunomodulating agents	Survived	94	94.9	6	66.7	80	100.0	**<.001**[†]
	Withdrawn	5	5.1	3	33.3	0	0.0	
M, musculoskeletal system	Survived	32	55.2	13	5.0	14	87.5	**.04**[‡]
	Withdrawn	26	44.8	13	5.0	2	12.5	
N, nervous system	Survived	132	70.2	61	64.9	63	81.8	**<.05**[δ]
	Withdrawn	56	29.8	33	35.1	14	18.2	
P, Antiparasitic products, insecticides & repellents	Survived	22	62.9	11	84.6	5	62.5	.34
	Withdrawn	13	37.1	2	15.4	3	37.5	
R, respiratory system	Survived	39	76.5	33	76.7	20	83.3	.78
	Withdrawn	12	23.5	10	23.3	4	16.7	
S, sensory organs	Survived	20	90.9	5	83.3	15	83.3	.75
	Withdrawn	2	9.1	1	16.7	3	16.7	
V, various	Survived	61	92.4	13	10.0	30	90.9	.55
	Withdrawn	5	7.6	0	.0	3	9.1	
Total[γ]		891	100.0	370	10.0	739	100.0	

[*] $P < .01$ for pure enantiomers *vs*. each of achiral drugs and chiral mixtures.
[†] $P = .02$ for chiral mixtures *vs*. achiral drugs and $P < .001$ for chiral mixtures *vs*. pure enantiomers.
[‡] $P = .02$ for pure enantiomers *vs*. each of achiral drugs and chiral mixtures.
[δ] $P = .02$ for pure enantiomers *vs*. chiral mixtures.
[γ] *Total count excludes withdrawn achiral drugs (n = 9), chiral mixtures (n = 3), and pure enantiomers (n = 12) with multiple or undefined ATC codes.*

greater therapeutic index.[19] The higher risks of withdrawal in achiral drugs (2.1-fold) and chiral mixtures (2.6-fold) compared to pure enantiomers in our study may suggest that such advantage seems to be reflected also into substantial ADRs that led to market withdrawal. This was also evident by our finding that showed prolonged survival of pure enantiomers (62.4 years) more markedly over chiral mixtures (52.4 years). In fact, the upward trend of chiral drugs appears to be mostly driven by up to 15-fold higher introduction of pure enantiomers over racemic mixtures between 2000 and 2008.[20] Higher rates of ADR-related withdrawal for chiral mixtures may have partly contributed to the increase in the development of pure enantiomers for the last decades. Indeed, the survival advantage of pure enantiomers over chiral mixtures in those launched between 1961 and 2000 disappeared for those launched afterwards, i.e., comparably younger drugs. While this might well be attributed to median TtW (ranged 15–20 years) in our study, another explanation could be the impact of the more rigorous safety-oriented assessments of drug development process. As of late 2000s, major drug authorities including the Food and Drug Administration and European Medicines Agency have required pharmaceutical companies to address specific safety issues both in premarketing and postlaunch phases as part of their marketing authorization.[21,22] This might have moderated the ADR-related withdrawal difference between young pure enantiomers and chiral mixtures. Additionally, drugs with different chiral characteristics in

TABLE 3 Comparison of chirality status of drugs leading to most common adverse drug reactions (n ≥ 30)

		Achiral		Chiral mixture		Pure enantiomer		
Adverse drug reactions	**Related withdrawal**	***n***	**%**	***n***	**%**	***n***	**%**	***P*-value**
Hepatotoxicity	No	848	94.2	352	94.4	747	99.5	**<.001**[*]
	Yes	52	5.8	21	5.6	4	0.5	
Cardiovascular	No	877	97.4	349	93.6	739	98.4	**<.001**[†]
	Yes	23	2.6	24	6.4	12	1.6	
Drug abuse	No	884	98.2	351	94.1	739	98.4	**<.001**[†]
	Yes	16	1.8	22	5.9	12	1.6	
Neurological	No	873	97.0	363	97.3	739	98.4	.17
	Yes	27	3.0	10	2.7	12	1.6	
Haematological	No	870	96.7	363	97.3	742	98.8	**.02**[‡]
	Yes	30	3.3	10	2.7	9	1.2	
Carcinogenicity	No	872	96.9	366	98.1	742	98.8	**0.03**[δ]
	Yes	28	3.1	7	1.9	9	1.2	
Dermatological	No	873	97.0	364	97.6	749	99.7	**<.001**[*]
	Yes	27	3.0	9	2.4	2	0.3	
Immunological	No	885	98.3	365	97.9	744	99.1	.24
	Yes	15	1.7	8	2.1	7	0.9	
Total		900	100.0	373	100.0	751	100.0	

[*]$P < .01$ for pure enantiomers *vs*. each of achiral drugs and chiral mixtures.
[†]$P < .01$ for chiral mixtures *vs*. each of achiral drugs and pure enantiomers.
[‡]$P < .01$ for pure enantiomers *vs*. achiral drugs.
[δ]$P = .01$ for pure enantiomers *vs*. achiral drugs.

TABLE 4 Comparison of time to withdrawal by chiral class for the most common adverse drug reactions (n ≥ 30)

	Achiral		Chiral mixture		Pure enantiomer		Total		
Adverse drug reactions (*n* ≥ 30)	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	***P*-value**
Hepatotoxicity ($n = 77$), y[a]	10	(2.3–21.5)	10	(5–17.5)	2	(1–14.3)	10	(3–18.5)	.32
Cardiovascular ($n = 59$), y[a]	7	(4–21)	23.5	(12–33)	21.5	(7–30.3)	18	(5–29)	**<.05**[*]
Drug abuse ($n = 50$), y[a]	23	(12.5–34.8)	29.5	(22.3–34.3)	27	(23–34.8)	26	(20.8–34.3)	.45
Neurological ($n = 49$), y[b]	23	(13–33)	8	(3.5–30)	25.5	(13.5–32.3)	22	(7.5–32.5)	.37
Haematological ($n = 49$), y[b]	22	(13.8–35.3)	11.5	(4–18.5)	25	(4–32)	20	(7–32)	.21
Carcinogenicity ($n = 44$), y[b]	15	(11.3–27.8)	12	(2–22)	12	(7.5–18)	15	(7.3–25.3)	.28
Dermatological ($n = 38$), y[a]	23	(9–35)	5	(2.5–11.5)	15	(8–22)	18	(6–28.3)	**.02**[†]
Immunological ($n = 30$), y[a]	31	(7–42)	11.5	(3.8–25.5)	20	(6–30)	19	(6.8–39)	.24

Abbreviation: IQR, interquartile range.
[a]Kruskal–Wallis test was used for statistical analyses.
[b]One-way analysis of variance (ANOVA) test was used for statistical analyses
[*]$P > .05$ for each of the multiple comparisons between pairs.
[†]$= .02$ for achiral drugs *vs*. chiral mixtures.

our study had similar durations to withdrawal and this pattern was mostly maintained in sub-analyses based on the most common ADRs (only with 1 exception in dermatological reactions).

The overall lower withdrawal rate of pure enantiomers was preserved across a number of drug groups at ATC-1 level. One of these belonged to the most commonly utilized drug group, nervous system drugs, with a 18.2% withdrawal rate in pure enantiomers compared to 35.1% in chiral mixtures. Nervous system drugs mainly require crossing the blood–brain barrier, which was reported to exert P-glycoprotein-mediated enantioselectivity for several drugs, leading to different brain concentrations.[23] Therefore, considering the advantageous situation regarding pure enantiomers in our study, it can be emphasized that the distribution and safety issues related to enantioselectivity of nervous system drugs and their relationship with their ability to cross

the blood–brain barrier should be addressed in more detail. Another group was musculoskeletal system drugs, where the rate of withdrawal was 12.5% for pure enantiomers *vs.* 50.0% for chiral mixtures. Musculoskeletal system drugs include a substantial part of nonsteroidal anti-inflammatory drugs (NSAIDs), whose majority is formed by racemates.[14,24] In fact, NSAIDs have been well-recognized to be associated with important safety issues that may result in withdrawal. A study on withdrawn drugs between 1960 and 1999 reported that 13% of such drugs were NSAIDs.[25] In fact, NSAIDs were among the most utilized drug groups.[26] This could suggest that putatively lower safety margin of chiral mixtures compared to pure enantiomer drugs may be associated with the emergence of important safety issues in frequently used medications. This might have been influenced to by possible over-the-counter or nonprescription use of these drugs as self-medication since we did not identify such difference in cardiovascular drugs, commonly used prescription medicines. The top 3 best-selling drugs in the USA in 2009 were reported to belong to the cardiovascular category and all were pure enantiomers.[20] In addition, chirality-related pharmacodynamic and pharmacokinetic characteristics of cardiovascular drugs were also extensively reviewed in the literature.[27] Nevertheless, our findings suggest that a potential relationship of chirality to withdrawal did not seem likely for cardiovascular mixed and pure enantiomers.

ADRs have a very wide range of potential causes, including chemical structure of the drugs, patient-related factors, and concomitantly used drugs or medicinal products.[28] Possible underlying causes trigger the incidence of drug-related problems of directly related tissues and organs. Hepatotoxicity, the most common type of ADR in our study, was the reason for withdrawal around 11-fold more likely in chiral mixtures and achiral drugs, compared to pure enantiomers. As the major organ for drug biotransformation, the liver holds the majority of drug metabolizing enzymes, which are chiral molecules. Due to stereoselectivity, each drug enantiomer may be metabolized through different pathways at different rates by these chiral enzymes.[29] As the metabolism of chiral mixtures may require different reactions for each of the individual isomers, this may raise the possibility of additional burden on the liver.[30] Furthermore, 1 of the critical components of drug-induced liver injury has been reported as drug biotransformation.[31] For instance, hepatotoxicity-related withdrawal of benoxaprofen, a racemic NSAID, was reported to be mediated by the formation of reactive acyl glucuronide metabolites.[32] While our data were not empowered to infer a causal association between chiral mixtures and liver injury, the tendency of racemic/nonracemic mixture drugs towards hepatotoxicity-driven withdrawal seems to have biological plausibility. This warrants designation of further detailed studies with specific racemic drugs to investigate such causal relationship. Another common reason for withdrawal, cardiovascular ADRs were also less frequently seen with pure enantiomers *vs.* achiral drugs and chiral mixtures, with the latter more marked. Although cardiovascular ADRs may also involve various mechanisms, a recent machine learning-based computational model study addressed biological binding and substructural chemical features of drugs in predicting cardiovascular ADRs.[33] The relative complexity of chiral mixtures might have contributed to observed high share of cardiovascular ADRs as a reason for withdrawal in our study. By contrast, median TtW was mostly maintained in subanalyses based on the most common ADRs (only with 1 exception in dermatological reactions). This suggests that temporality of different types of ADRs does not seem to be related to chiral characteristics of the drugs.

The results of the study should be interpreted considering its limitations below. Chirality details of some drugs/medicinal products included in the publication which was used to determine the drugs withdrawn between 1950 and 2014 could not be accessed. This resulted in a partial reduction in the number of products evaluated. For the comparative group, however, we searched all World Health Organization/ATC drug database and included all the universe of small-molecule drugs that could possess a chiral/achiral characteristic, excluding only those for which we could not reach the data of approval/marketing year or those approved throughout the year 2020. Another limitation was that ADRs that led to the withdrawal of the evaluated drugs were obtained directly from the sources used to identify the drugs, so these should not be considered as first-hand findings. In addition, we did not examine the severity or types of withdrawal-triggering toxicities in detail, e.g., in terms of dose-related, bizarre or delayed toxicity. Although out of scope of this study, dose-related events could have an impact on withdrawals considering the varying effective concentrations of racemates and enantiomers in different compartments of the body. Nevertheless, the chiral characteristics-based design of the study should not suggest that examined drugs were withdrawn from the market solely due to their stereochemical properties. We aimed to point out the possible effect of chirality on the distribution of ADRs, which should be further addressed by detailed future studies.

In conclusion, this study revealed that pure enantiomers were less likely to be withdrawn compared to chiral mixtures and achiral drugs. The survival advantage over chiral mixtures was mostly pronounced for the oldest drugs and those launched between 1961 and 2000. The chiral distribution of the withdrawn drugs could differ according to the usage areas and the underlying reasons for withdrawal. Chiral mixtures showed higher rates of withdrawal if they were in certain drug groups, including anti-infectives, or nervous, musculoskeletal or gastrointestinal system drugs. These drugs also seem to have tendency towards hepatotoxicity, cardiovascular, abuse-related and dermatological ADRs. The potential relationships between stereochemical properties of drugs and ADR mechanisms should be investigated with further experimental and epidemiological studies, which might indicate potential areas of improvements in safety standards for new drug development processes.

ACKNOWLEDGEMENTS

We thank to Dr Igho Onakpoya and his coworkers for their tremendous efforts and earlier studies on withdrawn drugs that inspired us to investigate another aspect of the subject. This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

COMPETING INTERESTS

The authors declare they have no competing or conflict of interest.

CONTRIBUTORS

V.A., A.B. and A.A. contributed to the study conceptualization and design. V.A., A.B. and C.V. collected the data. Analyses were performed by V.A., C.V. and A.B. The first draft of the manuscript was written by V.A., A.B. and C.V. A.A. contributed to the critical review and supervision of the study. All authors read and approved to the final version of the manuscript prior to submission.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Ahmet Akici https://orcid.org/0000-0002-8593-0818

REFERENCES

1. McConathy J, Owens MJ. Stereochemistry in Drug Action. *Prim Care Companion J Clin Psychiatry*. 2003;5(2):70-73. doi:10.4088/pcc.v05n0202
2. Abram M, Jakubiec M, Kaminski K. Chirality as an important factor for the development of new antiepileptic drugs. *Chem Med Chem*. 2019;20(14):1744-1761. doi:10.1002/cmdc.201900367
3. Smith SW. Chiral toxicology: it's the same thing...only different. *Toxicol Sci*. 2009;110(1):4-30. doi:10.1093/toxsci/kfp097
4. Hancu G, Modroiu A. Chiral switch: between therapeutical benefit and marketing strategy. *Pharmaceuticals (Basel)*. 2022;15(2):240. doi:10.3390/ph15020240
5. Chmielewska A, Konieczna L, Bączek T. A novel two-step liquid-liquid extraction procedure combined with stationary phase immobilized human serum albumin for the chiral separation of cetirizine enantiomers along with M and P parabens. *Molecules*. 2016;21(12):1654. doi:10.3390/molecules21121654
6. Tillement JP, Testa B, Brée F. Compared pharmacological characteristics in humans of racemic cetirizine and levocetirizine, two histamine H1-receptor antagonists. *Biochem Pharmacol*. 2003;66(7):1123-1126. doi:10.1016/s0006-2952(03)00558-6
7. Blaschke G, Kraft HP, Fickentscher K, Köhler F. Chromatographic separation of racemic thalidomide and teratogenic activity of its enantiomers. *Arzneim-Forsch*. 1979;29(10):1640-1642.
8. Tokunaga E, Yamamoto T, Ito E, Shibata N. Understanding the thalidomide chirality in biological processes by the self-disproportionation of enantiomers. *Sci Rep*. 2018;8(1):17131. doi:10.1038/s41598-018-35457-6
9. Agranat I, Caner H. Intellectual property and chirality of drugs. *Drug Discov Today*. 1999;4(7):313-321. doi:10.1016/s1359-6446(99)01363-x
10. Gal J. New single-isomer compounds on the horizon. *CNS Spectr*. 2002;7(4 Suppl 1):45-54. doi:10.1017/S1092852900028601
11. Tucker GT. Chiral switches. *Lancet*. 2000;355(9209):1085-1087. doi:10.1016/S0140-6736(00)02047-X
12. Onakpoya IJ, Heneghan CJ, Aronson JK. Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: a systematic review of the world literature. *BMC Med*. 2016;14(1):10. doi:10.1186/s12916-016-0553-2
13. Harding SD, Armstrong JF, Faccenda E, et al. The IUPHAR/BPS guide to PHARMACOLOGY in 2022: curating pharmacology for COVID-19, malaria and antibacterials. *Nucleic Acids Res*. 2022;50(D1):D1282-D1294. doi:10.1093/nar/gkab1010
14. WHO Collaborating Centre for Drug Statistics Methodology, ATC classification index with DDDs, 2022. Oslo, Norway 2021. https://www.whocc.no/atc_ddd_index/ Accessed 19 May 2022.
15. Siramshetty VB, Grishagin I, Nguyễn ĐT, et al. NCATS Inxight Drugs: a comprehensive and curated portal for translational research. *Nucleic Acids Res*. 2022;50(D1):D1307-D1316. doi:10.1093/nar/gkab918
16. Wishart DS, Feunang YD, Guo AC, et al. DrugBank 5.0: a major update to the DrugBank database for 2018. *Nucleic Acids Res*. 2018;46(D1):D1074-D1082. doi:10.1093/nar/gkx1037
17. Nguyen LA, He H, Pham-Huy C. Chiral drugs: an overview. *Int J Biomed Sci*. 2006;2(2):85-100.
18. Caner H, Groner E, Levy L, Agranat I. Trends in the development of chiral drugs. *Drug Discov Today*. 2004;9(3):105-110. doi:10.1016/s1359-6446(03)02904-0
19. Lennard MS. Clinical pharmacology through the looking glass: reflections on the racemate vs enantiomer debate. *Br J Clin Pharmacol*. 1991;31(6):623-625. doi:10.1111/j.1365-2125.1991.tb05583.x
20. Lin GQ, Zhang JG, Cheng JF. Overview of Chirality and Chiral Drugs. In: Lin GQ, Zhang JG, Cheng JF, eds. *Chiral Drugs: Chemistry and Biological Action*. 1st ed. John Wiley & Sons, Inc; 2011:3-28. doi:10.1002/9781118075647.ch1
21. Greener M. First do no harm. Improving drug safety through legislation and independent research. *EMBO Rep*. 2008;9(3):221-224. doi:10.1038/embor.2008.17
22. Corrigan-Curay J, Sacks L, Woodcock J. Real-world evidence and real-world data for evaluating drug safety and effectiveness. *JAMA*. 2018;320(9):867-868. doi:10.1001/jama.2018.10136
23. Choong E, Dobrinas M, Carrupt PA, Eap CB. The permeability P-glycoprotein: a focus on enantioselectivity and brain distribution. *Expert Opin Drug Metab Toxicol*. 2010;6(8):953-965. doi:10.1517/17425251003789394
24. Agranat I, Caner H, Caldwell J. Putting chirality to work: the strategy of chiral switches. *Nat Rev Drug Discov*. 2002;1(10):753-768. doi:10.1038/nrd915
25. Fung M, Thornton A, Mybeck K, Wu JH, Hornbuckle K, Muniz E. Evaluation of the characteristics of safety withdrawal of prescription drugs from worldwide pharmaceutical markets-1960 to 1999. *Drug Inf J*. 2001;35(1):293-317. doi:10.1177/009286150103500134
26. Inotai A, Hankó B, Mészáros Á. Trends in the non-steroidal anti-inflammatory drug market in six Central-Eastern European countries based on retail information. *Pharmacoepidemiol Drug Saf*. 2010;19(2):183-190. doi:10.1002/pds.1893
27. Ranade VV, Somberg JC. Chiral cardiovascular drugs: an overview. *Am J Ther*. 2005;12(5):439-459. doi:10.1097/01.mjt.0000167429.37357.0c
28. Alomar MJ. Factors affecting the development of adverse drug reactions (Review article). *Saudi Pharm J*. 2014;22(2):83-94. doi:10.1016/j.jsps.2013.02.003
29. Gross AS, Somogyi A, Eichelbaum M. Stereoselective Drug Metabolism and Drug Interactions. In: Eichelbaum M, Somogyi A, eds. *Stereochemical Aspects of Drug Action and Disposition. Handbook of Experimental Pharmacology* (Vol. 153, pp. 313-339). Berlin: Springer; 2003. doi:10.1007/978-3-642-55842-9_13.
30. Faber K, Griengl H. Chirality in Organic Synthesis — The Use of Biocatalysts. In: Janoschek R, ed. *Chirality*. Berlin: Springer; 1991:103-140.
31. European Association for the Study of the Liver. EASL clinical practice guidelines: Drug-induced liver injury. *J Hepatol*. 2019;70(6):1222-1261. doi:10.1016/j.jhep.2019.02.014
32. Walgren JL, Mitchell MD, Thompson DC. Role of metabolism in drug-induced idiosyncratic hepatotoxicity. *Crit Rev Toxicol*. 2005;35(4):325-361. doi:10.1080/10408440590935620

33. Jamal S, Ali W, Nagpal P, Grover S, Grover A. Computational models for the prediction of adverse cardiovascular drug reactions. *J Transl Med*. 2019;17(1):171. doi:10.1186/s12967-019-1918-z

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Aydin V, Bahar A, Vizdiklar C, Akici A. The association of chiral characteristic with drug withdrawal due to safety: A comparative analysis. *Br J Clin Pharmacol*. 2023;89(1):290-298. doi:10.1111/bcp.15486