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Investigation of the Cost Impact of Chirality Status of the Most Commonly Consumed Drugs in Turkey

Türkiye'de En Sık Tüketilen İlaçların Kiralite Durumunun Maliyete Yansımasının İncelenmesi

Ahmet AKICI[1], Caner VIZDIKLAR[1], Şeyhmus GAVAŞ[1], Nazım HASPOLAT[2], Dieudonne HAVYARİMANA[1], Selcan TÜLÜ ÇOLAK[1], Volkan AYDIN[3]

[1]Marmara University School of Medicine, Department of Medical Pharmacology, İstanbul, Turkey
[2]Bursa Uludağ University School of Medicine, Department of Medical Pharmacology, Bursa, Turkey
[3]İstanbul Medipol University International School of Medicine, Department of Medical Pharmacology, İstanbul, Turkey

Öz

Kiralite, terapötik veya advers etkiler yönünden ilaç aktivitesini etkileyen faktörler arasındadır. Yeni ilaç geliştirilmesinde, bu kavram doğrultusunda daha fazla fayda sağladığı düşünülen saf enantiyomer ilaçlar tavsiye edilmiştir. Bu çalışmada Türkiye'de sık tüketilen ilaçların kiralite durumları ve bunların maliyete yansımaları incelendi. Çalışmada IQVIA Türkiye biriminden alınan satış verileri kullanılarak ülke genelinde en fazla satılan ilk 200 etkin madde değerlendirildi ve 173'ünün kiralite durumu tespit edildi. Bu ilaçlar "kiral karışım", "akiral" ve "saf enantiyomer" olmak üzere üç gruba ayrılmalarının ardından kiralite durumlarına göre dağılımları ve ortalama kutu başına düşen (KBD) maliyetleri incelendi. Kiral dönüşümün maliyete yansımasını incelemek amacıyla dönüşüme uğrayan kiral karışımlarla bu işlem sonucunda meydana gelen saf enantiyomerler bu parametreler yönünden karşılaştırıldı. Kiralite durumu incelenen 173 etkin maddenin %35.8'i akiral, %22.0'ı kiral karışım ve %42.2'si saf enantiyomerdi. Toplam maliyet 2.09 milyar $ iken, maliyetin %46.4'ünü saf enantiyomerler, %22.0'ını ise kiral karışımlar oluşturmaktaydı. KBD maliyet ortalamaları bakımından saf enantiyomerler (2.8±3.5 $), akiral ilaçlar (2.3±2.5 $) ve kiral karışımlar (1.7±0.9 $) istatistiksel olarak benzerdi (p>0.05). Kiral dönüşüme uğrayan ilaçlarda kiral karışımların ortalama KBD maliyeti (1.4±0.4 $), saf enantiyomerlerinki (1.7±1.2 $) ile benzerdi (p>0.05). Kiral dönüşüme uğrayan ilaçların yarısında KBD maliyeti, kiral karışımda daha yüksekken diğer yarısında ise saf enantiyomerde daha yüksekti. Bu çalışmada Türkiye'de en çok satan ilaçlar arasında saf enantiyomerlerin önemli ölçüde yer tuttuğu ortaya konuldu. Sık kullanılan saf enantiyomer ve kiral karışımların maliyet yönünden benzer olması, saf enantiyomerlerin piyasada tercih edilme durumunun devam edebileceğini düşündürmektedir.

Anahtar Kelimeler: İlaç Harcamaları, Kiralite, Kiral Dönüşüm Kiral Karışım, Saf Enantiyomer

Abstract

Chirality is among the factors impacting drug activity in terms of therapeutic or adverse effects. Pure enantiomeric drugs, presumed to offer greater benefits in accordance with this concept, have been recommended for new drug development. We aimed to analyse the chirality status of the commonly consumed drugs in Turkey and assess their cost implications. We evaluated top-selling 200 active substances using nationwide sales data from IQVIA Turkey, identifying chirality status of 173. These were categorized into "chiral mixtures", "achiral", and "pure enantiomers", and their distribution and mean cost per unit (CPU) values by chirality status were examined. To examine the impact of chiral switching on expenses, CPUs of chiral-switched mixtures and resulting pure enantiomers, were compared. Among 173 compounds, 35.8% were achiral, 22.0% were chiral mixtures and 42.2% were pure enantiomers. Total cost was $2.09b, with pure enantiomers accounting for 46.4% and chiral mixtures 22.0%. Mean CPUs for pure enantiomers ($2.8±3.5), achiral drugs ($2.3±2.5), and chiral mixtures ($1.7±0.9) were similar (p>0.05). For drugs that underwent chiral switching, mean CPU of chiral mixtures ($1.4±0.4) was similar to that of pure enantiomers ($1.7±1.2), (p>0.05). Half of the chiral pairs that underwent switching had higher CPU for chiral mixture, while the other half had higher CPU for pure enantiomer. We demonstrated that pure enantiomers occupy a significant portion of top-selling drugs in Turkey. The observed cost similarity between commonly used pure enantiomers and chiral mixtures suggests that pure enantiomers may continue to gain preference in the market.

Keywords: Drug Expenditure, Chirality, Chiral Switch, Chiral Mixture, Pure Enantiomer

Introduction

Chirality, defined as the property of a molecule being non-superimposable on its mirror image, is among the important geometric properties of objects in biological systems (1). Each of a chiral molecule and its mirror image is called an enantiomer. Chiral compounds may consist of a single enantiomer or a mixture of two enantiomers, including racemates, which are 50:50 mixtures (2). The proportion of pure enantiomers in newly approved drugs has gradually increased over the years, and recent studies have reported that more than two-fifths of drugs on the market are pure enantiomers (3,4). In contrast to chiral molecules, molecules that can superimpose on their mirror image are defined as "achiral" (2).

In medicines that are present as chiral mixtures, each enantiomer may exhibit different levels of activity in terms of therapeutic or adverse effects. The variability in activity has also been linked to adverse reactions associated with one enantiomer of a drug, as

	ORCID No
Ahmet AKICI	0000-0002-8593-0818
Caner VIZDIKLAR	0000-0002-9558-1914
Şeyhmus GAVAŞ	0000-0002-2691-6485
Nazım HASPOLAT	0009-0004-8064-0346
Dieudonne HAVYARİMANA	0000-0002-4818-6313
Selcan TÜLÜ ÇOLAK	0000-0002-6383-7591
Volkan AYDIN	0000-0002-8511-6349

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Adres / Correspondence : Volkan AYDIN
Department of Medical Pharmacology, İstanbul Medipol University International School of Medicine, İstanbul, Turkey
e-posta / e-mail : volkan.aydin@medipol.edu.tr

evidenced by the thalidomide tragedy (5,6). Consequently, this observation has prompted the view that drugs composed of a single enantiomer might more effectively achieve the desired outcomes with fewer side effects (7). Pharmaceutical regulatory authorities such as the US Food and Drug Administration (FDA) have also recommended, although not mandated, the development of new drugs as pure enantiomers (8). In this context, the process of chiral switch, i.e. development of a single enantiomer from a chiral drug that has been marketed as a chiral mixture, has been initiated (4). The theoretical advantages of a chiral switch include lower dosage requirements for treatment, less variation in individual drug response, prevention of adverse effects potentially due to an inactive enantiomer, and a competitive advantage in the market (9). However, there are also arguments that chiral switch practices do not always yield significant benefits in clinical practice (10). While there are studies reporting a higher cost burden associated with pure enantiomeric drugs compared to chiral mixtures, due to the additional steps required in drug development, there are also opinions suggesting that the cost differences between drugs in different chiral statuses may diminish with increased mass production (11-13). In order to assess the impact of these developments on the chirality of medicines, it is necessary to identify how these practices affect consumption trends in the pharmaceutical market and the resulting financial burden. This study aimed to analyse the chirality status of the most commonly consumed drugs in Turkey and their impact on costs.

Material and Method

This study evaluated the chirality and chiral switch status of the most commonly used drugs in Turkey, along with their impact on consumption and costs. The study was initiated following the approval of İstanbul Medipol University Non-Interventional Clinical Studies Ethics Committee (approval number: 565, approval date: 23.06.2022).

The study utilized nationwide pharmaceutical sales data for 2021 at the wholesale level (i.e., sale from pharmaceutical warehouses to community pharmacies), obtained from the Turkey office of IQVIA (14). The 200 active substances with the highest number of units sold as single-ingredient preparations throughout the year were evaluated. Among these, inorganic substances, proteins, polymers, herbal products, vaccines, epimers, and products whose chirality status could not be evaluated (n=26) were excluded. The data regarding cefuroxime and its prodrug, cefuroxime axetil, which were listed as separate drugs in the dataset, have been combined for evaluation as a single active substance. After these steps, the remaining 173 active substances were included in the study (Figure 1).

The active substances were assigned into one of the three categories according to their chirality status: “achiral”, “chiral mixture” or “pure enantiomer”. The chirality status of the drugs were determined using the information in the US National Center for Advancing Translational Sciences (NCATS) Inxight Drugs database on 1-15 September 2022 (15). Of these active substances, the total number of single-ingredient preparations registered in the Turkish Medicines and Medical Devices Agency (TMMDA) database during the same timeframe were identified. Additionally, the distribution of the number of units (i.e., boxes) sold and their costs was analysed by chirality status of the active substances (16). The cost per unit (CPU) values of the active substances, based on their wholesale price, were calculated using the average US Dollar ($) exchange rate for the year 2021 (17).

The distribution of the number and CPU of active substances by chirality status, both overall and stratified at the first level of the Anatomical Therapeutic Chemical classification (ATC-1) by World Health Organization (WHO) were assessed (18). In addition, these assessments were also specifically made for certain widely used drug groups (acid suppressants, antidiabetics, antihypertensives, dermatological preparations, systemic antibiotics, analgesics [analgesic/anti-inflammatory/antirheumatics], antidepressants and systemic antihistamines). The consumption levels of the drugs were standardized according to “Defined Daily Dose” (DDD) parameter established by the WHO, in order to minimize the effect of differences in package contents on these results. For this purpose, the consumption and DDD values per unit were determined according to the chirality status of the active substances with an assigned DDD value in milligrams (89.0%). Among the drugs included in the study, the chirality status of the top 20 best-selling drugs and their costs were also analysed in more detail at ATC-5 level (18).

In order to examine the implications of chiral switch on drug expenses; sales volumes, costs, the number of single-ingredient preparations registered in TMMDA database, and the approval years of the first-registered preparations were compared (16). This analysis included chiral mixtures known to undergo chiral switching (n=8) and pure enantiomers produced by chiral switching (n=5) against their respective chiral counterparts. The active substances constituting the chiral pairs were categorized based on the list of the drugs under the ATC/DDD system (19). Of the 13 drugs analysed, six were included in the study alongside their chiral counterparts, while the remaining seven were included solely as chiral mixtures or pure enantiomers. Specifically, for this analysis, the chiral counterparts of these seven active substances were also included (Figure 1). In addition, a subgroup comparison was conducted for oral solid formulations of chiral drug pairs with assigned DDD

values to evaluate standardized consumption levels along with CPU. In order to calculate the consumed DDD levels for oral solid formulations, the number of units sold was multiplied by the strength and the number of tablets per pack of the preparations, and then divided by the DDD value assigned to the active substance.

Statistical analyses were performed using IBM SPSS 29.0 and GraphPad Prism 10.0 software. Data were expressed as numbers and percentages for categorical variables and mean ± standard deviation or median with interquartile range (IQR) for continuous variables. The Shapiro-Wilk test was used to determine whether the data was normally distributed. Depending on the presence of normal distribution, either Student's t-test or Mann-Whitney U test was used to compare continuous variables between two groups. Kruskal-Wallis test was employed for comparing more than two groups as the relevant data were not normally distributed. Type 1 error values below 0.05 were considered statistically significant.

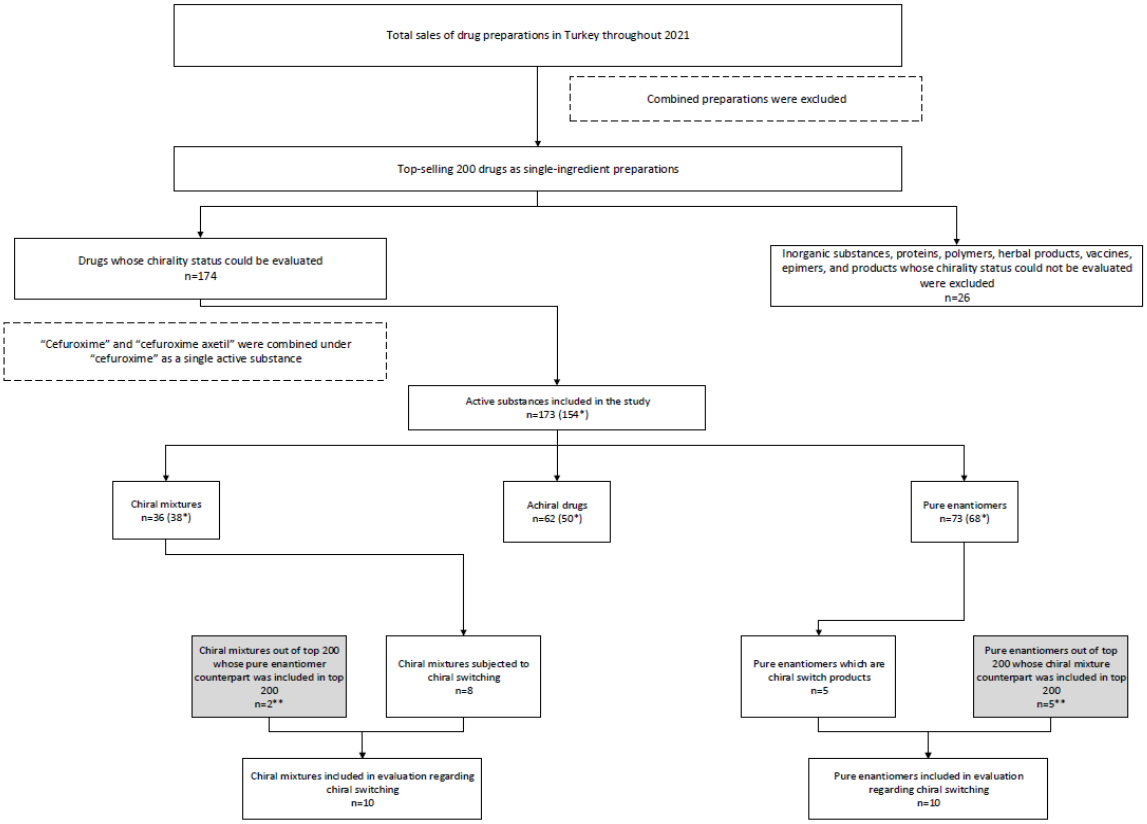

Figure 1. Flowchart of the study.
*: active substances with assigned DDD values. **: active substances not among top-selling 200 drugs but included in the study only for chiral switch analyses

Results

Of the 173 active substances examined in the study, 35.8% (n=62) were achiral, 22.0% (n=38) were chiral mixtures, and 42.2% (n=73) were pure enantiomers. The total number of units sold for all the active substances was 1,259,296,936, with achiral drugs comprising 37.9% of them. The total consumption of drugs with a defined DDD value was 29,163,894,917.9 DDD, with pure enantiomers accounting for 56.7% of this consumption. While the total cost of all drugs examined was $2.09 billion, pure enantiomers accounted for 46.4% of the cost, and chiral mixtures for 22.0% (Figure 2).

The means of CPU values of pure enantiomers ($2.8±3.5; median: 1.5, IQR: 1.0-2.3), achiral drugs ($2.3±2.5; median: 1.5, IQR: 1.1-1.9), and chiral mixtures ($1.7±0.9; median: 1.7, IQR: 1.2-2.4) were statistically similar ($p>0.05$ in pairwise comparisons). In seven of the 13 ATC-1 classes examined, pure enantiomers produced the highest CPU. The ATC-1 class in which pure enantiomers yielded the highest CPU was "S-Sensory organs". The greatest CPU difference among the chiral categories was observed in "C-Cardiovascular system" where achiral drugs were more expensive than pure enantiomers. In "P-Antiparasitic products" class, both achiral drugs and chiral mixtures were found to be more expensive than pure enantiomers (Table 1).

The top 20 largest-selling pharmaceuticals accounted for 46.5% of the total number of units

sold and 29.7% of the total cost. Of the units sold, 26.5% were achiral drugs, 33.0% were mixtures, and 40.5% were pure enantiomers. In terms of total cost, achiral drugs accounted for 40.3%, mixtures for 28.2%, and pure enantiomers for 31.5%. Based on the number of packages sold, the most commonly sold drug was paracetamol, constituting 7.1% of all pharmaceuticals examined. The drug generating the highest cost was diclofenac, accounting for 3.1% of the total cost of all drugs examined. Both the top-selling and the highest-costing drugs were achiral (Supplementary Table 1). When the examined pharmaceuticals were categorized into widely-used pharmacological drug groups, it was observed that achiral drugs were most prevalent in analgesics (60.0%), chiral mixtures in antihypertensives (62.5%), and pure enantiomers predominantly in systemic antibiotics (73.9%). In four of these eight groups, pure enantiomers generated the highest CPU, whereas in three groups, chiral mixtures generated the highest CPU. In antidiabetics, which had the highest CPU ($4.1), pure enantiomers were the chiral category with the highest cost ($8.3) (Table 2).

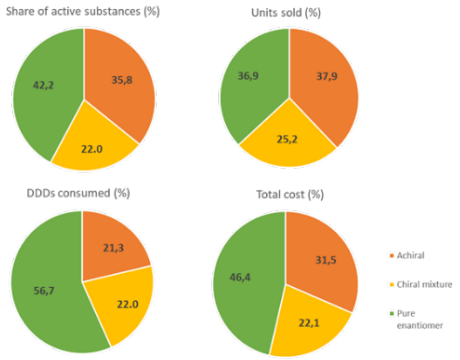

Figure 2. Distribution, sold units, consumed defined daily doses (DDDs), and total costs of top-selling active substances in Turkey by chirality status.
**Only active substances with known DDD values were included (n=154).*

Table 1. Distribution and cost per unit of top-selling active substances in Turkey by chirality status at the first level of Anatomical Therapeutic Chemical (ATC) classification.

	Total			Achiral			Chiral mixtures			Pure enantiomers			Delta -1**	Delt a-2***
ATC-1 classes	n	% (%)*	Cost per unit (US $)	n	% (%)*	Cost per unit (US $)	n	% (%)*	Cost per unit (US $)	n	% (%)*	Cost per unit (US $)		
A – Alimentary tract and metabolism	28	100.0 (16.2)	2.1	9	32.1 (14.5)	1.7	7	25.0 (18.4)	1.6	12	42.9 (16.4)	2.7	+1.1	+1.0
N – Nervous system	24	100.0 (13.9)	1.7	13	54.2 (21.0)	1.4	5	20.8 (13.2)	1.8	6	25.0 (8.2)	2.6	+0.8	+1.2
C – Cardiovascular system	22	100.0 (12.7)	1.7	4	18.2 (6.5)	2.3	10	45.5 (26.3)	1.6	8	36.3 (11.0)	1.6	0	-0.7
J – Antiinfectives for systemic use	20	100.0 (11.6)	1.4	5	25.0 (8.1)	1.3	1	5.0 (2.6)	1.6	14	70.0 (19.2)	1.4	-0.2	+0.1
R – Respiratory system	21	100.0 (12.1)	1.5	9	42.9 (14.5)	1.5	5	23.8 (13.2)	1.3	7	33.3 (9.6)	1.8	+0.5	+0.3
M – Musculo-skeletal system	17	100.0 (9.8)	1.0	8	47.1 (12.9)	1.0	5	29.4 (13.2)	1.1	4	23.5 (5.5)	1.1	0	+0.1
D - Dermatologicals	16	100.0 (9.3)	1.7	9	56.2 (14.5)	1.9	2	12.5 (5.3)	1.4	5	31.3 (6.8)	1.5	+0.1	-0.4
B – Blood and blood forming organs	7	100.0 (4.0)	1.6	2	28.6 (3.2)	0.9	1	14.3 (2.6)	1.1	4	57.1 (5.5)	3.5	+2.4	+2.6
G – Genitourinary system and sex hormones	7	100.0 (4.0)	4.5	1	14.3 (1.6)	4.5	1	14.3 (2.6)	1.4	5	71.4 (6.8)	5.1	+3.7	+0.6
H – Systemic hormonal preparations	5	100.0 (2.9)	1.1	-	-	-	-	-	-	5	100.0 (6.8)	1.1	NA	NA
S – Sensory organs	4	100.0 (2.3)	7.3	2	50.0 (3.2)	3.4	-	-	-	2	50.0 (2.7)	11.4	NA	+4.1
L – Antineoplastic and immunomodulating agents	1	100.0 (0.6)	3.8	-	-	-	-	-	-	1	100.0 (1.4)	3.8	+3.8	0
P – Antiparasitic products	1	100.0 (0.6)	1.9	-	-	-	1	100.0 (2.6)	1.9	-	-	-	-1.9	-1.9
Total	173	100.0 (100.0)	1.7	62	100.0 (35.8)	1.4	38	100.0 (22.0)	1.5	73	100.0 (42.2)	2.1	+0.6	+0.4

*: Column percentage. **: Cost per unit difference between pure enantiomers and chiral mixtures. ***: Cost per unit difference between pure enantiomers and achiral drugs.

When the DDD values of achiral drugs, chiral mixtures, and pure enantiomer drugs were examined, the percentage distribution of these values was found to be 21.3%, 22.0%, and 56.7%, respectively (Figure 2).

Among the active substances examined, a total of 13 (7.5%) were involved in chiral switching process, including 8 chiral mixtures (amlodipine, cetirizine, citalopram, ibuprofen, ketoprofen, lansoprazole, rabeprazole, and salbutamol) and 5 pure enantiomers (dexketoprofen, esomeprazole, escitalopram,

levocetirizine, and levodropropizine). These pharmaceuticals accounted for 10.1% of the total number of units sold and 10.5% of the total cost. There were six chiral drug pairs in which both the chiral mixture and the pure enantiomer forms were available on the market. Among the chiral drug pairs that involved in switching, there were three gastric acid suppressants, two analgesics, one antidepressant, one antihypertensive, one beta-2 agonist, one antihistamine, and one antitussive (Figure 3). Among the drugs that underwent chiral switching, the pure enantiomer preparations of three (dexibuprofen, S-amlodipine, dexlansoprazole) and the preparation of dropropizine, the form before chiral switching of levodropropizine, were registered in the TMMDA database; however, the 2021 IQVIA sales data did not record any sales data for these drugs.

Table 2. Distribution and cost per unit of selected drug groups among top-selling active substances in Turkey, categorized by chirality status.

	Total			**Achiral**			**Chiral mixtures**			**Pure enantiomers**			**Delta -1****	**Delta-2*****
Drug groups	n	% (%)*	Cost per unit (US $)	n	% (%)*	Cost per unit (US $)	n	% (%)*	Cost per unit (US $)	n	% (%)*	Cost per unit (US $)		
Systemic antibiotics	18	100.0 (10.4)	1.3	3	21.1 (1.6)	1.1	1	5.2 (2.6)	1.6	14	73.9 (19.2)	1.4	-0.2	+0.3
Drugs used to treat hypertension (C03-C09)	16	100.0 (9.2)	1.6	2	12.5 (3.2)	1.4	10	62.5 (26.2)	1.6	4	25.0 (5.5)	1.3	-0.3	-0.1
Dermatologicals (D)	16	100.0 (9.2)	1.7	9	53.3 (12.7)	2.1	2	13.4 (5.3)	1.4	5	33.3 (6.8)	1.5	+0.1	-0.6
Analgesics/Anti-inflammatories / Antirheumatics	15	100.0 (8.7)	0.9	9	60.0 (14.3)	0.8	4	26.7 (10.5)	1.0	2	13.3 (2.7)	1.1	+0.1	+0.3
Drugs used to treat depression (N06)	10	100.0 (5.8)	1.8	3	20.0 (3.2)	1.4	4	40.0 (10.5)	2.0	4	40.0 (5.5)	1.9	-0.1	+0.5
Drugs used in diabetes (A10)	8	100.0 (4.6)	4.1	2	25.0 (3.2)	1.7	2	25.0 (5.5)	2.3	4	50.0 (5.5)	8.3	+6.0	+6.6
Antihistamines for systemic use	8	100.0 (4.6)	1.5	4	50.0 (6.3)	1.5	3	37.5 (7.9)	1.3	1	12.5 (1.4)	1.8	+0.5	+0.3
Drugs for acid related disorders (A02)	7	100.0 (4.1)	1.3	2	28.6 (3.2)	1.2	3	42.8 (7.9)	1.2	2	28.6 (4.0)	1.3	+0.1	+0.1
Others	75	100.0 (43.4)	2.1	19	39.5 (47.6)	2.9	9	11.8 (23.7)	1.5	37	48.7 (50.7)	2.4	+0.9	-0.5
Total	173	100.0 (100.0)	1.7	63	36.2 (100.0)	1.4	38	21.8 (100.0)	1.5	73	42.0 (100.0)	2.1	+0.6	+0.7

: Column percentage. **: Cost per unit difference between pure enantiomers and chiral mixtures. *: Cost per unit difference between pure enantiomers and achiral drugs.*

Although the pure enantiomer formulations of three drugs that are chiral switch products (dexibuprofen, S-amlodipine, and dexlansoprazole) and the pre-chiral switch form of levodropropizine (dropropizine) were listed in the TMMDA database, no sales data for these drugs were recorded in the 2021 IQVIA sales data. Among the remaining six chiral drug pairs, it was observed that the consumption of rabeprazole, cetirizine, and salbutamol, both in terms of the number of units sold and the cost, was higher than that of the pure enantiomers of these drugs. In contrast, the opposite was observed for the other three chiral pairs (i.e., escitalopram, esomeprazole, and dexketoprofen were predominant) (Figure 3). The time periods between the approval of the first preparations of chiral mixtures and their pure enantiomer counterparts varied, ranging from 2 to 37 years. For the chiral mixtures that are predominant in terms of sales and costs, the average time to switch to pure enantiomers and the number of preparations were 20.0±14.7 years and 28.7±11.0 preparations, respectively, while for predominant pure enantiomers, these averages were 17.7±14.6 years and 70.7±36.6 preparations (Table 3).

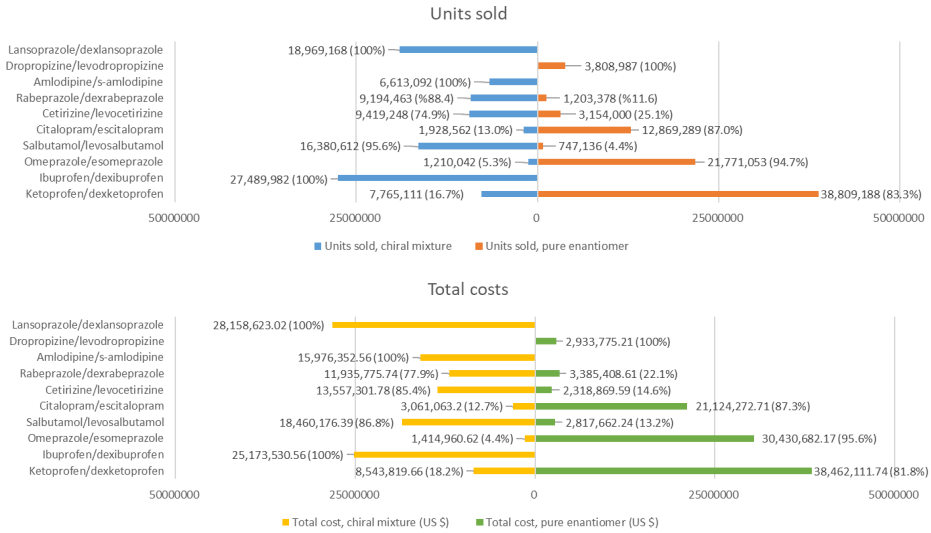

Figure 3. Units sold and total costs of active substance pairs subjected to chiral switching.

For chiral drug pairs with both chiral mixtures and pure enantiomer formulations were available in Turkey, the average CPU of chiral mixtures ($1.4±0.4) was similar to that of pure enantiomers ($1.7±1.2 USD), (p>0.05). In half of these chiral drug pairs, the CPU was higher for chiral mixture, while in the other half, it was higher for pure enantiomer. There was no statistically significant difference in the average number of preparations between chiral mixtures and pure enantiomers (45.7±30.7 vs. 36.7±39.1, p>0.05) (Table 3).

When the oral solid formulations of chiral drug pairs were compared, an increase in consumption after chiral switching was observed in the pure enantiomers of all pharmaceuticals except levocetirizine, with the highest increase seen in esomeprazole (approximately 24-fold) (Table 4).

The distribution of top-selling drugs by chirality status was found to be similar to that of the recent global drug market, especially with regard to pure enantiomers (3). Previous studies have revealed that the market share of pure enantiomer drugs was around one-quarter in the 1990s and increased to three-eighths by 2005 (2,20). The 42.2% share in our study, along with the 56.7% consumption by DDD amount for pure enantiomers, indicates a growing trend in the market share of these formulations. A previous study listed various factors influencing the high sales of a drug, including order of entry and quality (21). It can be considered that the leadership of pure enantiomers in sales figures in our study is not solely related to chirality. In fact, the majority of the 73 pure enantiomers among the most consumed drugs were originally introduced to the market in their current form. This might be related to the potential influence of recommendations and trends for producing new drugs as pure enantiomers on the most frequently preferred drugs in the market. In accordance with recommendations from various health authorities, particularly the FDA, to develop new pharmaceuticals as pure enantiomers whenever possible, a study published in 2000 predicted that consumption of pure enantiomers could increase by as much as 8% annually (22). The predominance of pure enantiomers among new pharmaceuticals introduced in subsequent years may be a contributing factor to this increase (20,23).

Table 3. Cost per unit values and number of single-ingredient preparations approved in Turkey for the drug pairs subjected to chiral switching.

Chiral mixture (Year**)	Cost per unit (US $)	No of approved preparations (%)*	Pure enantiomer (Year**)	Cost per unit (US $)	No of approved preparations (%)*	Delta 1***	Delta 2****
Ketoprofen (1975)	1.10	24 (25.3)	Dexketoprofen (2006)	0.99	73 (74.7)	-0.11	31
Ibuprofen (1973)	0.92	100 (98.0)	*Dexibuprofen* (2009)	NA	2 (2.0)	NA	36
Omeprazole (1991)	1.17	23 (41.1)	Esomeprazole (2011)	1.40	33 (58.9)	0.23	20
Salbutamol (1975)	1.13	36 (97.3)	*Levosalbutamol* (2012)	3.77	1 (2.7)	2.64	37
Citalopram (2003)	1.59	38 (26.4)	Escitalopram (2005)	1.64	106 (73.6)	0.05	2
Cetirizine (1996)	1.44	34 (63.0)	Levocetirizine (2008)	0.74	20 (37.0)	-0.70	12
Rabeprazole (2002)	1.30	16 (94.1)	*Dexrabeprazole* (2013)	2.81	1 (5.9)	1.51	11
Amlodipine (1991)	2.42	95 (97.9)	*S-amlodipine* (2011)	NA	2 (2.1)	NA	20
Dropropizine (-)	NA	NA	Levodropropizine (2000)	0.77	23 (100.0)	NA	NA
Lansoprazole (1996)	1.48	45 (91.8)	*Dexlansoprazole* (2012)	NA	4 (8.2)	NA	16

Active substances not among top-selling 200 drugs were italicized. * Percentage among all preparations of the chiral drug pair (i.e., of both chiral mixture and pure enantiomer). ** Year of approval for the first approved preparation. *** Difference between cost per unit values of chiral mixture and pure enantiomer of the chiral drug pair. **** Difference between the years of approval for the first approved preparations of chiral mixture and pure enantiomer of the chiral drug pair.

Discussion

This study, which investigated the chiral characteristics of the 200 most frequently used drugs in Turkey, revealed that pure enantiomers hold the highest share, consumption level, and cost among the 173 active substances where stereoisomerism could be examined. The fact that nearly one out of every two pharmaceuticals is a pure enantiomer, coupled with similar findings when this descriptive analysis was narrowed to the top 20 most commonly used pharmaceuticals, suggests that these drugs are widely preferred in clinical practice.

In our study, no significant difference was found among the three chirality categories in terms of CPU. Considering that pure enantiomers are generally more expensive than chiral mixtures (24,25), this unexpected result might be influenced by factors such as local pricing of medical formulations, the scope of drug-specific promotional activities, and the number of generic drugs. The high number of generics for commonly used active substances might have obscured the CPU differences between drugs. Indeed, in our study, for commonly used drugs with chiral pairs, 24 and 73 preparations were identified for ketoprofen and dexketoprofen, 23 and 33 for omeprazole and esomeprazole, and 38 and 106 for citalopram and escitalopram, respectively. This situation, combined with the strict drug price control policy in Turkey (26), may have contributed to the fact that the higher costs of pure enantiomers reported in the literature were not reflected in our study. Another reason could be the optimization of the production processes for pure enantiomers over time. While more complex steps were required to purify chiral mixtures when synthetic production of pure enantiomers was still new, the innovation and increasing optimization of new purification methods such as crystallization, chromatography, membrane-based chiral separation, and biochemical reactions may have helped close the cost gap between chiral mixtures and pure enantiomers (27,28).

Table 4. Distribution of units sold, consumption, and cost figures of the drug pairs subjected to chiral switching.

Active substance (DDD*) Total units sold (%) Total consumed DDD (%)	Chiral switch	Strength	Tablets per pack	Units sold (%)	Consumed DDD (%)	Cost	
						Per unit	Per DDD
Cetirizine (10)	Before	10	10	1,312,248 (20.1)	13,122,480.0 (11.2)	0.9	0.09
6,519,852 (100)		10	20	5,207,604 (79.9)	104,152,080.0 (88.8)	1.7	0.08
117,274,560.0 (100)							
Levocetirizine (5)	After	5	20	3,121,426 (99.0)	62,428,520.0 (98.0)	0.9	0.04
3,154,000 (100)		5	40	32,574 (1.0)	1,302,960.0 (2.0)	1.6	0.03
63,731,480.0 (100)							
Citalopram (20)	Before	20	28	1,576,924 (81.8)	44,153,872.0 (68.5)	1.4	0.05
1,928,562 (100)		20	56	21,864 (1.1)	1,224,384.0 (1.9)	2.3	0.04
64,485,176.0 (100)		40	28	318,353 (16.5)	17,827,768.0 (27.6)	2.3	0.04
		40	56	11,421 (0.6)	1,279,152.0 (2.0)	1.0	0.01
Escitalopram (10)	After	5	28	897,803 (7.1)	12,569,242.0 (4.8)	1.3	0.10
12,713,071 (100)		10	28	7,430,657 (58.4)	7,430,657.0 (2.9)	1.5	0.05
260,303,347.0 (100)		10	56	175,852 (1.4)	9,847,712.0 (3.8)	2.9	0.05
		10	84	28,136 (0.2)	2,363,424.0 (0.9)	4.5	0.05
		15	28	907,780 (7.1)	38,126,760.0 (14.6)	3.1	0.07
		20	28	3,188,584 (25.1)	178,560,704.0 (68.6)	1.5	0.03
		20	56	75,474 (0.6)	9,928,968.0 (3.8)	3.4	0.03
		20	84	8,785 (0.1)	1,475,880.0 (0.6)	5.6	0.03
Omeprazole (30)	Before	20	14	212,351 (17.6)	2,972,914.0 (9.6)	0.7	0.11
1,209,852 (100)		20	28	997,501 (82.4)	27,930,028.0 (90.4)	1.3	0.11
30,902,942.0 (100)							
Esomeprazole (30)	After	20	14	321,279 (1.5)	2,998,604.0 (0.4)	0.6	0.11
2,177,089 (100)		28	28	1,086,710 (5.0)	20,285,253.0 (2.6)	1.3	0.11
776,949,291.0 (100)		40	14	350,870 (1.6)	6,549,573.0 (0.9)	0.7	0.11
		40	28	20,012,032 (91.9)	747,115,861.0 (96.2)	1.4	0.11
Ketoprofen (150)	Before	100	20	1,515,025 (42.0)	20,200,333.3 (49.2)	1.3	0.09
3,603,148 (100)		150	10	2,088,123 (58.0)	20,881,230.0 (50.8)	1.3	0.13
41,081,563.3 (100)							
Dexketoprofen (75)	After	25	20	33,146,478 (84.4)	22,149,832.0 (71.8)	0.9	0.13
37,489,757 (100)		50	30	4,343,279 (11.6)	86,865,580.0 (28.2)	1.8	0.09
109,015,412.0 (100)							

* DDD value assigned by the World Health Organization.

The reflection of chiral switch process to the pharmaceutical market emerged as another important finding in our study. However, the debate about the practical benefits of chiral switching for commonly used drugs that are currently available as chiral mixtures is still ongoing (24). The fact that four out of the ten chiral drug pairs included in the study—both their chiral mixtures and pure enantiomers—are among the top-selling drugs nationwide suggests that the practical benefits of chiral switch products are not adequately reflected in the preferences of physicians and patients. As a previous study indicated, this may be due to factors such as competitive pricing and various similar drug marketing strategies (29). When an alternative to well-established drugs enters the market, even if it offers potential tangible advantages,

the brand effect created by general marketing, the brand value generated by the commercial name, and the longstanding preferences of physicians and patients pose substantial barriers to significant changes. This might account for why pure enantiomers developed through chiral switching do not completely replace older chiral mixtures in the Turkish market. Our study showed that except omeprazole, the market share of the top-selling chiral mixtures subjected to chiral switching did not dramatically decrease to the extent that they would fall out of the top 200 drugs. Indeed, three chiral drug pairs were able to remain among the top 200 most consumed drugs, both as chiral mixture and pure enantiomer. It might be argued that commercial name and brand equity, along with the familiarity of the active substance, have facilitated the establishment of these drugs' presence in the market. Consequently, as new versions of drugs that have undergone chiral switching emerge, their established brand recognition may help them maintain market presence despite competition from potentially superior alternatives. It is expected that the development of new drugs undergoing chiral switching will benefit from these experiences. On the other hand, the extent to which this observation made in frequently used drugs applies to less commonly used ones might be the subject of future research.

The cost increase in drugs that have undergone chiral switching becomes even more pronounced when considering factors such as their classification as new drugs, protection from generic competition, and the clinical research and licensing procedures involved (30). For these reasons, while an increase in costs might be expected after chiral switching, our study found no statistically significant difference in cost per DDD or CPU. It should be kept in mind that our analysis of chiral switching was conducted with the most frequently consumed drugs in the country. Given the large market share of such frequently consumed drugs, it can be considered that the cost increase associated with their status as new drugs has been cushioned by marketing strategies and even partially reversed to maintain financial competition. From this perspective, our study does not support the claim that products of chiral switching generate higher costs compared to their chiral mixtures. The observed situation in frequently used drugs and its possible relationship with marketing strategies could be a subject for future studies to determine whether this is applicable to less frequently used drugs undergoing chiral switching.

It was noteworthy that pure enantiomers predominated in 6 out of 13 ATC-1 classes, with "H-Systemic hormonal preparations" and "L-Antineoplastics and immunomodulating agents" consisting entirely of pure enantiomers. This predominance might be potentially related to these groups containing a relatively higher number of newer drugs. Indeed, it is known that a significant portion of new drug research is primarily focused on treatments for cancer and endocrine-related diseases (31-33). Our study also revealed that the ATC-1 class with the highest CPU produced by pure enantiomers is "S-Sensory organs". A similar finding in a previous study conducted in Turkey was attributed to the small number of generic drugs in this class (34). The high cost of pure enantiomers in sensory organ drugs, as revealed in this study, might be associated with the higher production, research, and development costs of these drugs, as well as the limited number of generic competitors in the market.

The findings of our study should be interpreted in light of the existing limitations. Firstly, drugs in Turkey are subject to price control policies. It should be considered that in cost comparisons of drug groups, differences based on chemical characteristics may not directly reflect the actual production costs. Additionally, the impact of regulations related to price control and drug marketing strategies on market dynamics was not evaluated in this study. Another limitation of our study was the exclusion of combination products. The decision to exclude was due to the complexity and difficulty of conducting analyses when the active substances involved belong to different chiral groups, making cost calculations more challenging.

Conclusion

This study demonstrated that pure enantiomers hold a significant position in the Turkish pharmaceutical market. The cost similarity between commonly used pure enantiomers and chiral mixtures, observed both in overall drugs and chiral switch products, indicates that pure enantiomers may continue to be increasingly preferred in the market in the future. Although the theoretical advantages of these pharmaceuticals in terms of efficacy and safety suggest a cost-benefit balance in favour of pure enantiomers, it should be noted that this study was conducted on the most commonly utilized pharmaceuticals. These findings need to be validated by future studies that encompass all drugs on the market and consider the social, economic, legal, and geographical factors influencing drug use.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

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References

1. McConathy J, Owens MJ. Stereochemistry in Drug Action. Prim Care Companion J Clin Psychiatry. 2003;5(2):70-3.
2. Hancu G, Modroiu A. Chiral Switch: Between Therapeutical Benefit and Marketing Strategy. Pharmaceuticals (Basel). 2022;15(2):240.
3. Aydin V, Bahar A, Vizdiklar C, et al. The association of chiral characteristic with drug withdrawal due to safety: A comparative analysis. Br J Clin Pharmacol. 2023;89(1):290-8.
4. 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, pp 3-28, 2011.
5. Agranat I, Wainschtein SR, Zusman EZ. The predicated demise of racemic new molecular entities is an exaggeration. Nat Rev Drug Discov. 2012;11(12):972-3.
6. Simoens S, De Bruyn K, Bogaert M, et al. Pharmaceutical policy regarding generic drugs in Belgium. Pharmacoeconomics. 2005;23(8):755-66.
7. Hutt AJ. The development of single-isomer molecules: why and how. CNS Spectr. 2002;7(S1):14-22.
8. Food and Drug Administration (FDA). FDA's policy statement for the development of new stereoisomeric drugs. Chirality. 1992;4(5):338-40.
9. Agranat I, Caner H. Intellectual property and chirality of drugs. Drug Discov Today. 1999;4(7):313-21.
10. Gellad WF, Choi P, Mizah M, et al. Assessing the chiral switch: approval and use of single-enantiomer drugs, 2001 to 2011. Am J Manag Care. 2014;20(3):e90-7.
11. Carlson SC. Commentary: the case against market exclusivity for purified enantiomers of approved drugs. Yale Symp L & Tech. 1999;6.
12. Pifferi G, Perucca E. The cost benefit ratio of enantiomeric drugs. Eur J Drug Metab Pharmacokinet. 1995;20(1):15-25.
13. Scarpignato C, Pelosini I, Di Mario F. Acid suppression therapy: where do we go from here? Dig Dis. 2006;24(1-2):11-46.
14. Kirmizi NI, Aydin V, Akici A. Utilization trend of gastric acid-suppressing agents in relation to analgesics. Pharmacoepidemiol Drug Saf. 2022;31(3):314-21.
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):D1307-16.
16. KÜB/KT Listesi. Türkiye İlaç ve Tıbbi Cihaz Kurumu (TİTCK). Access date: 27 May 2024. https://www.titck.gov.tr/kubkt
17. EVDS Anasayfa. Türkiye Cumhuriyeti Merkez Bankası (TCMB). Access date: 30 May 2024. https://evds2.tcmb.gov.tr/
18. ATC Classification. World Health Organization (WHO). Access date: 12 Dec 2024 https://www.who.int/tools/atc-ddd-toolkit/atc-classification
19. ATC/DDD Index. World Health Organization (WHO). Access date: 27 May 2024, https://atcddd.fhi.no/atc_ddd_index/
20. Single-Enantiomer Drugs Poised for Further Market Growth. Pharmaceutical Technology. Access date: 6 June 2024, https://www.pharmtech.com/view/single-enantiomer-drugs-poised-further-market-growth
21. Fischer M, Leeflang PSH, Verhoef PC. Drivers of peak sales for pharmaceutical brands. Quant Mark Econ. 2010;8(4),429-60.
22. Stinson SC. Chiral Drugs. Chem. Eng. News. 2000;78(43),55-78.
23. McVicker RU, O'Boyle NM. Chirality of New Drug Approvals (2013-2022): Trends and Perspectives. J Med Chem. 2024;67(4):2305-20.
24. Long AS, Zhang AD, Meyer CE, et al. Evaluation of Trials Comparing Single-Enantiomer Drugs to Their Racemic Precursors: A Systematic Review. JAMA Netw Open. 2021;4(5):e215731.
25. Mansfield P, Henry D, Tonkin A. Single-enantiomer drugs: elegant science, disappointing effects. Clin Pharmacokinet. 2004;43(5):287-90.
26. 10 Temmuz 2015 Tarihli ve 29412 Sayılı Resmî Gazetede yayımlanan 2015/7752 Sayılı Beşeri Tıbbi Ürünlerin Fiyatlandırılmasına Dair Karar. Türkiye İlaç ve Tıbbi Cihaz Kurumu (TİTCK). Access date: 07 October 2024. https://www.titck.gov.tr/faaliyetalanlari/ilac/ilacta-fiyatlandirma#:~:text=E%C5%9F%20de%C4%9Fer%20%C3%BCr%C3%BCn%C3%BCn%20piyasa%20%C3%A7%C4%B1kmas%C4%B1,%80'ine%20kadar%20olabilir
27. Ciriani M, Oliveira RM, Afonso CA. Semi-continuous and continuous processes for enantiomeric separation. Green Chem. 2022;24(11),4328-62.
28. Kaspereit M, Swernath S, Kienle A. Evaluation of Competing Process Concepts for the Production of Pure Enantiomers. Org. Process Res. Dev. 2012;16(2),353-63.
29. Khoso I, Ahmed RR, Ahmed J. Pricing strategies in pharmaceutical marketing. Pharma Innovation. 2014;3(7):13-7.
30. Calcaterra A, D'Acquarica I. The market of chiral drugs: Chiral switches versus de novo enantiomerically pure compounds. J Pharm Biomed Anal. 2018;147:323-40.
31. Brown DG, Wobst HJ. A Decade of FDA-Approved Drugs (2010-2019): Trends and Future Directions. J Med Chem. 2021;64(5):2312-38.
32. Dahlén AD, Dashi G, Maslov I, et al. Trends in Antidiabetic Drug Discovery: FDA Approved Drugs, New Drugs in Clinical Trials and Global Sales. Front Pharmacol. 2022;12:807548.
33. Scott EC, Baines AC, Gong Y, et al. Trends in the approval of cancer therapies by the FDA in the twenty-first century. Nat Rev Drug Discov. 2023;22(8):625-40.
34. Tuna E, Yenilmez FB, Atikeler K, Kockaya G. Discount distribution analysis of original medicines which has no generics in Turkey. Value Health. 2015;18(7):A547.