Health Policy 97 (2010) 71–78

Contents lists available at ScienceDirect

Health Policy

journal homepage: www.elsevier.com/locate/healthpol

The discrepancy in attention deficit hyperactivity disorder (ADHD) medications diffusion: 1994–2003—A global pharmaceutical data analysis

Hui-Chu Lang[a,*,1], Richard M. Scheffler[b,c], Teh-wei Hu[c]

[a] Institute of Hospital and Health Care Administration, National Yang-Ming University, No.155, Sec. 2, Li-Nong St., Taipei 112, Taiwan
[b] The Nicholas C. Petris Center on Health Care Markets and Consumer Welfare, United States
[c] University of California, Berkeley, United States

ARTICLE INFO

Keywords:
International
Health policy
ADHD
Drug expenditure
Pharmacoeconomics

ABSTRACT

Objective: The purpose of this paper was to examine the patterns of spending, price, and the utilization of ADHD medications during the 10-year period, from1994 to 2003 among 4 different per capita GDP group countries.
Methods: This study used the IMS Health database and included both branded and generic ADHD medications. We examined the changes in quantity and price as well as the mixed effects of these changes in the U.S.A. and 3 other groups of countries classified according to their level of per capita GDP.
Results: During this study (1994–2003), the U.S. expenditures for ADHD medications increased 594%; sales volume rose by 80%; and price increased by 285%. In other high GDP countries, expenditures increased 493%, sales volume 328%, and price increased by 39%. In the middle GDP countries, expenditures increased 164%, sales volume 141%, and price increased by 9%. In the countries with a lower per capita GDP, expenditures increased 149%, sales volume 464%, however price decreased by 37%.
Conclusions: The launch of long-acting ADHD medications has dramatically increased the total medication expenditure in the U.S. as well as in other high GDP markets. In the other countries quantity was the most important growth factor.

1. Introduction

Attention deficit hyperactivity disorder (ADHD), the most commonly diagnosed behavioral/mental health disorder in children, affects 3–12% of world's children [1]. It was defined in the diagnostic and statistical manual of mental disorders (DSM-III) as attention deficit disorder with hyperactivity (ADD-H) in 1980 [2] and was renamed ADHD in the 1987 edition of the DSM-manual (DSM-III-R) [3]. The 2000 edition (DSM-IV-TR) [4] provides very similar lists of symptoms as the ICD-10 [5] criteria but recommends different ways of establishing a diagnosis. The ADHD prevalence rates based on DSM-IV are far higher than those of the hyperkinetic disorder of ICD-10 [6,7].

Comparing prevalence rates of ADHD is not straightforward because diagnostic criteria vary over time, and strongly affects the estimates of the number of children with and without ADHD. In addition, a number of variables including the assessment methods as well as the individuals reporting the behavioral symptoms, the population sampled, the diagnostic criteria applied, and the sex of the affected individual may affect the estimates. To look at the prevalence of ADHD internationally, Faraone et al.

* Corresponding author. Tel.: +886 2 2826 7015; fax: +886 2 2820 6252.
E-mail addresses: hclang@ym.edu.tw (H.-C. Lang), rscheff@berkeley.edu (R.M. Scheffler), thu@berkeley.edu (T.-w. Hu).
[1] This paper was written while Dr. Lang was an AHRQ post-doc fellow at UC Berkeley.

0168-8510/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.healthpol.2010.03.005

[8] systematically reviewed 50 papers published between the years 1982 and 2001 and found no significant difference between the prevalence of this disorder in the U.S. compared to most other countries or cultures (most were European countries and cultures) if they applied the DSM diagnosis criteria. The latest broad and systematic review by Polanczyk confirmed that after adjusting for methodological differences, there were no significant differences in the ADHD/HD prevalence rates between North America and Europe [9].

Few studies have explored the factors that determined the growth in U.S. pharmaceutical expenditures. Dubois et al. [10] were pioneers in analyzing the spending on prescription drugs. They disaggregated the total spending between 1994 and 1997 into several price and volume factors, identifying substantial spending increases ranging from 43% to 219% for seven disease categories. They found that, although prices rose in every case, the growth in volume greatly exceeded price in its impact on spending. In fact, the relative ratios of increased volume to increased price ranged from a low of 2.5:1 for hormone replacement therapy to over 10:1 for gastrointestinal agents and lipid-lowering drugs. Berndt's study [11,12] of the growth in annual U.S. pharmaceutical spending between 1994 and 2000 reached conclusions that were consistent with those of Dubois. Berndt found a 12.9% growth in spending. Of this, 20% was directly attributable to price increases, while nearly 80% was related to increased utilization. He found that price increases were relatively less important than the growth in the quantity being used, the primary driver behind the increase in expenditures.

Despite public attention and the controversy surrounding the increased use of ADHD medications, there is no published research that compares global expenditures, pricing, and usage. The purpose of this paper was to examine the patterns of spending, price, and utilization of ADHD medications for the 10-year period, 1994–2003 in different wealthy countries around the globe. We categorized the countries in this study as U.S., high GDP countries, middle GDP countries and low GDP countries and compared their ADHD expenditures over time in order to determine the relative extent to which expenditures are to be attributed to price, quantity, or to a mix of price and quantity among those groups.

2. Methods

2.1. Data

Data from the IMS Health database was employed to analyze ADHD medication trends from a global perspective during the study period. IMS Health is the world's leading provider of market intelligence to the pharmaceutical and healthcare industries. The company receives data from more than 139,000 data suppliers covering 730,000 individual dispensing sites, in more than 100 countries for the past 50 years. Data sources include drug manufacturers, wholesalers, retail pharmacies, hospitals, long-term care facilities and healthcare professionals, http://www.imshealth.com/portal/site/imshealth. To extract the drugs used, we adapted the three-digit anatomical therapeutic chemical classification (ATC) system. ADHD medications include those in the ATC = N6B psychostimulants category, along with the non-amphetamine-like stimulants modafinil (Provigil) and atomoxetine HCL (Strattera). Both branded and generic drugs within those categories were retrieved from the database. The medications from the IMS dataset were further examined by clinical experts using the molecular formula, international product name, and local product name to define the medications and remove any that were not used in ADHD treatment. The international product name is defined by IMS Health. It matches products from different countries if they have the same manufacturer or brand-name, and eliminates licensed products from the originator sold under a different brand-name. Countries with at least one standard unit of sales of the defined medications were included in the study.

2.2. Measures

The range and mix of the dosage form, strength, and pack size differs significantly across countries. In this study a standard unit (SU) was adopted to determine the sales volume. The standard unit is the number of standard dose units sold. It is determined by taking the total number of counting units sold and divide it by the standard unit factor, which is the smallest common dose of a product form as defined by IMS Health. Using a standard unit is the best way to compare drugs within a therapeutic class that has a mixture of forms (solids, liquid, injectable, etc.). One SU is equivalent to one 5-mg tablet, 5 mL of a liquid, or one injectable vial. For example, a 20-mg tablet is counted as four SUs (Table 1).

The study used the standard unit average price (price per dose) at the ex-manufacturer level (wholesale purchase level). The average price in a country was defined as the volume-weighted average price per SU for all products. All non-U.S. currency was converted to U.S. dollars, using the current exchange rates. To eliminate the inflation effect over the study's 10-year period, we deflated the dollars by each country's Consumer Price Index (CPI 2000 = 100), which was extracted from the World Bank Group WDI online database http://devdata.worldbank.org/dataonline/.

Since countries across the globe vary substantially in their GDP (gross domestic product), we divided the countries in our study into four groups by per capita GDP. The U.S. which dominates the market in ADHD medications (accounting for more than 80% of the world sales volume) [13] was treated as a single group. The other countries were divided into three groups according to their per capita GDP adjusted by PPP (Purchasing Power Parity; World Bank data). For those countries that have a per capita GDP higher than USD 30,000 were categorized as high GDP countries, of which there were 21. For those countries with a per capita GDP less than USD 10,000, they were categorized as low GDP countries, of which there were 14. The other 15 countries belonged to the middle GDP countries (see Appendix 1).

Table 1
ADHD new medication approved by FDA.

Stimulants			Other stimulants		
Product name	Company	Approval date	Product name	Company	Approval date
Long-acting					
Concerta	ORTHO MCNEIL JANSSEN	08/01/2000; 12/08/2000; 04/01/2002	Pemoline	In 2005, FDA withdrew approval for pemoline	
Metadate CD	UCB INC.	04/03/2001; 06/19/2003; 05/27/2003; 02/19/2006	Cylert	In 2005, FDA withdrew approval for pemoline	
Ritalin LA	NOVARTIS	06/05/2002; 04/10/2004	Modafinil	RANBAXY LAB.	02/08/2004; 01/07/2004
Adderall XR	SHIRE	10/11/2001; 05/22/2002	Provigil	CEPHALON	12/24/1998
Dextroamphetamine (Dexedrine Spansule)	BARR	01/18/2002; 01/31/2001		Non- stimulants	
	MALLINCKRODT	05/06/2003	Strattera	LILLY	11/26/2002; 02/14/2005
	OUTLOOK PHARMS	01/29/2008			
	MALLINCKRODT	01/29/2002			
	KV PHARM	10/31/2002			
Short-acting					
Metadate ER	UCB INC	10/20/1999			
Ritalin and Ritalin-SR	NOVARTIS	06/05/ 2002; 04/10/2004			
Adderall	SHIRE	10/11/2001; 05/22/2002			
	DURAMED RES	08/31/2000			
Dextroamphetamine (Dexadrine)	BARR	01/18/2002; 01/31/2001			
	MALLINCKRODT	05/06/2003			
	OUTLOOK PHARMS	01/29/2008			

Source: FDA orange book http://www.fda.gov/cder/ob/default.htm.

2.3. Model

The fluctuations in drug expenditure can be expressed through price and quantity indicators. However, these two components alone cannot explain all of the consumer behavior, because it does not take into account the variation produced by new drugs that are licensed, new formulations, or the shift toward more innovative products [14]. Since most of the innovative long-acting ADHD medications were approved after 1999, we divided the 10-year study period into the before-1999 period and the after-1999 period. This allowed us to examine the effect of new drugs on expenditure growth. Disaggregating the spending trends allowed us to analyze the underlying clinical and economic drivers of the spending [15]. In this study we proposed an additive model to analyze the data.

Additive model

$$\frac{\Delta E}{E} = \frac{\Delta P}{P} + \frac{\Delta Q}{Q} + \left(\frac{\Delta P}{P} \times \frac{\Delta Q}{Q}\right) \quad (1)$$

where E denotes expenditure, P denotes price, and Q denotes quantity. The change in expenditure $\Delta E/E$ equals the change in quantity $\Delta Q/Q$ plus the change in price $\Delta P/P$ plus the residual ($\Delta P/P \times \Delta Q/Q$).

To examine the changes in the global and individual country expenditure of ADHD medications from 1994 to 2003, we separated the percent expenditure change in E (i.e., $\Delta E/E$) into three components: the percent change in quantity Q (i.e., $\Delta Q/Q$); the percent change in price P (i.e., $\Delta P/P$); and the product ($\Delta P/P \times \Delta Q/Q$) of the percent change in quantity and the percent change in price (26) [16].

The average price in a country was defined as the volume-weighted average price per SU for all products. The third component included the combined changes of price and quantity, called the residual factor. This combined factor can be affected by the improved quality of the product, insurance coverage, cost containment, pharmaceutical advertising, drug innovation, and other factors. We compared the global, U.S., and the markets of the OECD countries over time. Due to the domination of the U.S. sales volume, unless explicitly stated, we separated the OECD countries and the U.S. in the analysis.

3. Results

3.1. Trends in expenditures, sales volume, and prices

Table 2 shows that in 1994, the global ADHD medication expenditure was USD 279 million in nominal dollars (data not shown). After converting to the 2000 constant U.S. dollars based on each country's consumer price index (CPI), the real global expenditure was $332 million. In 1999, global expenditures increased to USD 720 million, and by 2003 this had increased to USD 2.26 billion. In the U.S. mar-

Table 2
ADHD medication expenditures, sales volume, and prices.

COUNTRY	E_{1994}_R (Million)	E_{1999}_R (Million)	E_{2003}_R (Million)	Q_{1994}_R (Million)	Q_{1999}_R (Million)	Q_{2003}_R (Million)	P_{1994}_R	P_{1999}_R	P_{2003}_R
Global Market	332	720	2258	958	1762	1956	0.35	0.41	1.15
U.S.	304	658	2110	851	1500	1530	0.36	0.44	1.38
High GDP country	22.2	54.1	131	84.9	223	364	0.26	0.24	0.36
Middle GDP country	5.53	7.41	14.6	19.5	32.0	47.1	0.28	0.23	0.31
Low GDP country	0.78	0.70	1.95	2.89	6.36	16.29	0.27	0.11	0.12

CPI 2000 = 100. E_{1994}_R: year 1994 ADHD medication expenditure in real dollars. Q_{1994}_R: year 1994 sales volume in standard unit. P_{1994}_R: year 1994 average price in real dollars.

ket, expenditures went from USD 304 million in 1994, to USD 658 million in 1999, and to USD 2.11 billion by 2003. In other high GDP countries, expenditures increased from USD 22.2 million in 1994, to USD 54.1 million in 1999, to USD 131 million in 2003. In the middle GDP countries, expenditures increased from $5.53 million in 1994, to USD 7.41 million in 1999, to USD 14.6 million in 2003. In the low GDP countries, expenditures increased from USD 0.78 million in 1994, to USD 0.70 million in 1999, to USD1.95 million in 2003.

Sales volume of ADHD medication in the global market was 958 million standard units in 1994; it increased to 1.76 billion SU in 1999, and to 1.96 billion SU in 2003. In the United States, the sales volume was 851 million SU in 1994, 1.5 billion SU in 1999, and 1.53 billion SU in 2003. The high DGP countries had a sales volume of 84.9 million SU in 1994, 223 million SU in 1999, and 364 million SU in 2003. The middle GDP countries had a sales volume of 19.5 million SU in 1994, 32.0 million SU in 1999, and 47.1 million SU in 2003. The low GDP countries had a sales volume of 2.89 million SU in 1994, 6.36 million SU in 1999, and 16.29 million SU in 2003. In terms of price, the average real price of ADHD medications for all countries was USD 0.35 per SU in 1994. In 1999 and 2003, the average prices increased to USD 0.41 and USD 1.15, respectively. In the U.S., the real average price per SU was USD 0.36 in 1994; it rose to USD 0.44 in 1999 and to USD 1.38 in 2003. For other high GDP countries, the average price per SU was USD 0.26 in 1994; rising to USD 0.24 in 1999 and to USD 0.36 in 2003. For the middle GDP countries, the average prices per SU were USD 0.28 in 1994, USD 0.23 in 1999, and USD 0.31 in 2003. For the low GDP countries, the average prices per SU were USD 0.27 in 1994, USD 0.11 in 1999, and USD 0.12 in 2003.

3.2. Regional comparison of expenditures in global, OECD, and U.S. markets

Our results show that from 1994 to 2003, the global ADHD medication expenditure increased by 758% in nominal dollars, or 579% in real dollars (Table 3). This suggests that inflation had a strong impact on the ADHD medication expenditure increase. The decomposition of the changes in quantity $\Delta Q/Q$ and price $\Delta P/P$ (additive model) shows that while the global sales volume increased by 104%, the price increased 233% in real dollars. The sales volume accounted for 18% of the total growth in expenditures, and the product price accounted for 40%. Due in part to the complexity of the global market across countries, the residual accounted for the largest part, 42%. U.S. expenditures increased 594% in real dollars. At the same time, the U.S. experienced an 80% increase in volume and a 285% increase in real average price. About 13% of the U.S. expenditure increase resulted from the sales volume increase; 48% was due to the real price increase; and 39% was explained by the residual. It is evident that prices in both the global and the U.S. markets changed more rapidly than the sales quantity during the 10-year study period.

The expenditure for high GDP countries increased 493%; sales volume rose by 328%, and price increased by approximately 39%. About 66% of the OECD expenditure increase was due to the increase in sales volume; 8% was due to real price increases; and the residual explained 26%. The expenditure for middle GDP countries increased 164%; sales volume rose by 141%, and price increased by approximately 9%. About 86% of the OECD expenditure increase was due to the increase in sales volume; 6% was due to price; and the residual explained 8%. The expenditure for the low GDP countries increased 149%; sales volume rose by 464%, and price decreased by approximately 56%. Although low GDP countries experienced much higher growth in ADHD medication sales volume, their price decreased.

The middle row section of the additive model in Table 3 shows the changes in medication expenditures, quantities, and prices between 1994 and 1999. During this period the expenditure, sales volume, and price did not increase as much as over the entire study period. The global expenditure increased 117% from 1994 to 1999, sales volume rose 84%, and price increased 18%. About 72% of the global expenditure increase was due to sales volume, 15% was due to the price, and the residual explained 13%. In the U.S. the expenditure grew 116%, sales volume rose 76%, and price increased 23%. About 66% of this increase was due to sales volume, 19% due to price, and 15% due to the residual.

High GDP countries increased 144% expenditures; sales quantity rose by 162%, however the price declined by 7%. The middle GDP countries increased their expenditures by 34% and their sales quantity by 64%. However, the price decreased by 18%. The low GDP countries decreased their expenditures by 11% and their price by 60%. However, their sales volume increased by 120%. During this period the major increase of the ADHD medication expenditure was due to the sales volume. All three groups except the U.S. all showed an increase in their prices. In sum, from 1994 to 1999, the quantity increase greatly exceeded the price increase except for the low GDP countries which showed a decrease in their expenditure.

Table 3
The results of the additive mode $\Delta E/E = \Delta P/P + \Delta Q/Q + (\Delta P/P \times \Delta Q/Q)$.

Country	$\Delta E_{(03-94)}/E_{94}$	$\Delta Q_{(03-94)}/Q_{94}$	$\Delta P_{(03-94)}/P_{94}$	$(\Delta P/P \times \Delta Q/Q)$	$\Delta E_{(99-94)}/E_{94}$	$\Delta Q_{(99-94)}/Q_{94}$	$\Delta P_{(99-94)}/P_{94}$	$(\Delta P/P \times \Delta Q/Q)$	$\Delta E_{(03-99)}/E_{99}$	$\Delta Q_{(03-99)}/Q_{99}$	$\Delta P_{(03-94)}/P_{94}$	$(\Delta P/P \times \Delta Q/Q)$
Global market	5.79	1.04 18%	2.33 40%	2.42 42%	1.17	0.84 72%	0.18 15%	0.15 13%	2.14	0.11 5%	1.82 85%	0.2 10%
U.S.A.	5.94	0.8 13%	2.85 48%	2.29 39%	1.16	0.76 66%	0.23 19%	0.17 15%	2.21	0.02 1%	2.14 97%	0.05 2%
High GDP (without U.S.)	4.93	3.28 66%	0.39 8%	1.27 26%	1.44	1.62	−0.07	−0.11	1.43	0.63 44%	0.49 34%	0.31 22%
Middle GDP	1.64	1.41 86%	0.09 6%	0.13 8%	0.34	0.64	−0.18	−0.12	0.97	0.47 49%	0.34 35%	0.16 16%
Low GDP	1.49	4.64	−0.56	−2.59	−0.11	1.2	−0.6	−0.72	1.8	1.56 87%	0.09 5%	0.15 8%

All the prices are in real terms: adjusting expenditure and price by the consumer price index (2000 = 100). E_{94}: ADHD medication expenditure of year 1994. P_{94}: ADHD medication price of year 1994. Q_{94}: consumption quantity of all ADHD medication in 1994. $\Delta E_{(03-94)}/E_{94} = \Delta E_{03} - E_{94}/E_{94}$.

The last row shows the changes in medication expenditures, quantities, and prices between 1999 and 2003. The global market expenditures increased 214%; sales volume rose 11%; and prices increased 182%. About 5% of the increase in the global market expenditure was due to sales volume; 85% was due to price; and 10% was due to the residual. The U.S. market showed the highest expenditures and rate of price increase during 1999–2003. Expenditures rose 221%, sales volume increased only 2%; and prices increased 214%. Only 1% of the rise in total ADHD medication expenditures in the U.S. was due to sales volume, 97% was due to price, and the residual explained 2%.

In the high GDP countries, expenditures increased 143% in real dollars, sales volume went up 63%, and price increased 49%. About 44% of the increase in total expenditures was due to sales volume, 34% was due to price, and the residual explained 22%. In the middle GDP countries, expenditures increased 97% in real dollars, sales volume went up 47%, and price increased 34%. About 49% of the increase in total expenditures was due to sales volume, 35% was due to price, and the residual explained 16%. In the low GDP countries, expenditures increased 180% in real dollars, sales volume went up 156%, and price increased by only 9%. About 87% of the increase in total expenditures was due to sales volume, 5% was due to price, and the residual explained 8%. During this period, low GDP countries had the highest percent sales volume increase.

4. Discussions

4.1. Changes in ADHD medication expenditures over time

Our results showed that U.S. has been the dominant market in the world in terms of ADHD medications expenditures in 1994. One country accounted for 91.6% of the global ADHD medication expenditure; other high GDP countries accounted for only 6.7%. The middle GDP and low GDP countries combined accounted for approximate 2% (Table 2). By the end of 2003, this had increased to 93.5% in the U.S., but had decreased to 5.8% in other high GDP countries. The middle and low GDP countries combined accounted for <1%. Given the increasing concern worldwide about ADHD treatment [17], this huge divergence should raise the alarm bell.

There are a couple of reasons that could explain this major discrepancy. The U.S. adopted the new DSM diagnosis criteria earlier than most European OECD countries, which might explain the high market share in ADHD medication spending. A cross country study provided the evidence that the estimates of prevalence in the U.S. have been historically higher than the U.K. estimates due to the narrower diagnostic criteria in ICD-10 which was used in the U.K. [18]. More U.S. children were diagnosed and treated earlier because in the US they used the DSM criteria earlier than in the U.K. Outside the U.S., in some cultures, children who have symptoms consistent with ADHD as defined by the DSM-IV, parents consider it a behavioral problem and will not consider it requiring any kind of treatment. Thus, the recognition of ADHD symptoms and labeling the child as being deviant or having a pathological

disorder depends on the norms of behavior accepted in a particular culture [19].

The difference in prescription guidelines may also have contributed to the discrepancy in the expenditures for ADHD medications between the U.S.A. and other countries. The guidelines of the American Academy of Pediatrics state that once diagnosis is made (any subtype), clinicians should recommend stimulant medication and/or behavior therapy [20]. In contrast, The National Institute for Clinical Excellence (NICE) recommends that methylphenidate be used for treatment of children with severe hyperkinetic disorder (broadly equivalent to the combined form of ADHD). This implies that stimulants should not be recommended for children with the inattentive and impulsive-hyperactive subtypes or for patients without a severe ADHD diagnosis [21].

In terms of expenditure growth rate over time, within the decade of our study (1994–2003), global ADHD medication expenditures increased 579%. The U.S. and other high GDP countries showed a soaring increase in the medication expenditures, which were 594%, 493% respectively, while the middle and low GDP countries had moderate increasing rates (164% and 149%) (Table 3). Comparing 1994–1999 with 1999–2003, the latter period had a higher rate of total expenditure increase than the former one in both the U.S. and low GDP countries (116% vs. 221%; −11% vs. 180%). The following volume and price decomposition analysis may provide more information to explain.

During the 10-year long study period, the volume of ADHD medication sales increased by 104% globally; 80% in the U.S. market, 328% in other high GDP countries, 141% in the middle GDP countries and 464% in the low GDP countries. These increase in the rates were all much higher than that of the U.S.A. Comparing 1994–1999 with 1999–2003, the U.S. showed a huge decline in the rate of increase of sales volume, from 76% to 2%, in spite of the soaring growth rate in expenditure. Except for the low GDP countries, high GDP countries and middle GDP countries also showed a decreasing rate of volume growth over these two periods.

In terms of price, the rate of increase in the U.S. showed a continuous growth and was substantially higher than the other three groups. In addition, the rate of the price increase was much higher in the second half of the study period (1999–2003) than in the first half (1994–1999). The other three groups of countries all showed a decrease in the price growth rate during the first period and an increase in the growth rate in the second period.

The U.S. market was already dominant prior to 1994, and there was relatively little room for increase. This helps explain why the increase in the rate of volume growth in the U.S. was lower compared to that of other countries. However, both the other high GDP countries and the middle GDP countries also experienced a declining rate of sales volume increase when comparing the increase rate of the second period to that of the first period. The timing fits with the FDA approval of new long-acting, often once-a-day ADHD medications after 1999 as shown in Table 1 and in other research [22]. Those newer branded medications have largely replaced short-acting stimulants as the most common pharmacological treatment for children and adolescents due to their significant clinical utility [23], especially in the U.S. We call it the "innovation effect." This change in medication pattern in the U.S. helps to explain the decreased rate of sales volume growth and the increased rate of price growth after 1999.

High pharmaceutical prices are mainly the result of a long, risky, and expensive research and development process that can last as long as 12–15 years. DiMasi et al. [24] estimated that the average cost of bringing a new drug to market to be $403 million in 2000 constant dollars. Accounting for the time between investment and marketing raises the cost to $802 million. U.S. patients are more willing to access health care technology than those in other developed countries. Most of the time, high technology means high price, an important factor in ADHD medication expenditure. The U.S. General Accounting Office (GAO) found that in 1993 the factory price of a market basket of 77 leading branded drugs, weighted by their volume of use in the U.S., was about 60% higher than in the U.K. [25]. Prices for brand-name prescription drugs were 35–55% lower in other industrialized countries than in the United States [26].

Our results also revealed the time lag for the diffusion of new technology among the different levels of wealthy countries. Our study also found that the increase in human capital increases the rate of technology catch-up, which is consistent with the findings of the study of Xu and Chiang [27] on the role of human capital in technology diffusion. High income countries adopt new technologies earlier than do the middle and low income countries. However, high income countries also pay a higher price for R&D and thus enjoy the new technology earlier. At the same time, middle and low income countries benefit from the technology spillovers from the wealthy countries.

In conclusion we can say that the international exploration of medication diffusion is important for the health of us all. Nevertheless, few studies have been conducted on this issue due to the limitation of data availability and the difficulty to make comparisons, because of the varied healthcare insurance systems and third party payment schemes being used. In the United States, the pricing of branded pharmaceuticals is determined primarily by demand. Many other countries have a national or regional purchasing governance with whom brand manufacturers negotiate a drug reimbursement price. This method, as well as a highly diverse range of mechanisms employed by countries to control the cost of pharmaceuticals explains some of the price differences across the OECD countries [28].

The price per standard unit adopted in the present study, allowed us to include all dosage forms, strength forms, and pack sizes for each product. It is more representative than restricting it to drugs that are sold by the same manufacturer and in the same dosage form and strength in all countries. This method allowed all drugs to be included in the comparison. A limitation of this study was that due to data availability, we could only obtain the price at the ex-manufacturer level (wholesale purchase level). Estimates

of ex-manufacturer prices are generally based on list prices published by manufacturers rather than on the actual selling, or transaction prices. Hence, it is an underestimation of the real costs to society.

5. Conclusion

The U.S. market accounted for the lion's share of the global ADHD medication sales volume during this 10-year study period. The gap between the U.S. and other countries is large enough to require the careful attention of policy-makers. In addition, prices for ADHD medications increased much faster in the U.S. than in other countries, both before and after 1999. The difference was even greater after 1999, when many of the novel ADHD drugs appeared on the market. To mitigate this effect in the future, U.S. payers, providers, and consumers should consider the cost-effectiveness of a medication when making decisions about drug acceptance and coverage.

Funding source

This study was funded in part by a grant from the National Institute for Mental Health (R01 MH067084), in part by a grant from The Center for Child and Youth Policy, University of California, Berkeley, and in part by The Nicholas C. Petris Center, School of Public Health, University of California, Berkeley.

Acknowledgments

The authors would especially like to thank Thomas Rice, Ph.D. for his critical comments on the earlier draft. We also like to thank Peter Levine, MD and Stephen P. Hinshaw, Ph.D. for identifying and categorizing the ADHD medications.

Appendix A. Country GDP and GDP ranking by IMF, WB and CIA.

Country	Rank	IMF	Rank	WB	Rank	CIA
Luxembourg	2	80,457	1	79,985	2	80,500
Norway	3	53,037	2	53,701	4	53,000
Singapore	5	49,714	3	50,299	6	49,700
United States	6	45,845	4	45,790	8	45,800
Ireland	7	43,144	5	42,978	9	43,100
Hong Kong	–	41,994	–	42,321	–	42,000
Switzerland	8	41,128	6	39,244	10	41,100
Netherlands	11	38,486	7	38,144	14	38,500
Canada	12	38,435	11	35,729	16	38,400
Austria	13	38,399	8	38,106	15	38,400
Sweden	16	36,494	12	35,622	19	36,500
Australia	17	36,258	14	34,882	20	36,300
Finland	18	35,280	13	35,124	22	35,300
Belgium	19	35,273	15	34,780	21	35,300
United Kingdom	20	35,134	16	34,105	23	35,100
Germany	21	34,181	18	33,450	24	34,200
Japan	22	33,577	17	33,525	26	33,600
France	23	33,188	19	33,281	27	33,200
Italy	25	30,448	23	29,981	29	30,400
Republic of China (Taiwan)	26	30,126	–	N/A	30	30,100
Spain	27	30,120	22	30,587	31	30,100
Greece	28	29,172	20	33,274	33	39,200
Slovenia	30	27,205	25	27,095	34	27,200
New Zealand	31	26,379	26	26,110	35	26,400
Israel	32	25,799	27	25,918	36	25,800
South Korea	34	24,783	28	24,712	39	24,800
Czech Republic	35	24,236	29	22,982	40	24,200
Saudi Arabia	37	23,243	30	22,907	42	23,200
Portugal	39	21,701	31	21,497	43	21,700
Slovakia	41	20,251	33	20,188	45	20,300
Hungary	43	19,027	34	18,912	47	19,000
Latvia	47	17,416	36	17,518	51	17,400
Poland	50	16,311	37	16,075	54	16,300
Russia	52	14,692	41	14,743	56	14,700
Chile	54	13,936	42	13,885	58	13,900
Malaysia	56	13,315	44	13,379	61	13,300
Argentina	57	13,308	46	13,244	60	13,300
Turkey	59	12,888	48	12,216	63	12,900
Mexico	60	12,775	47	12,780	64	12,800
Venezuela	62	12,166	49	12,168	66	12,200
Uruguay	63	11,621	55	11,236	67	11,600
South Africa	76	9,761	62	9,736	81	9,800
Brazil	78	9,695	63	9,570	82	9,700
Thailand	81	7,900	68	8,138	86	7,900
Peru	83	7,803	69	7,842	87	7,800

Appendix A *Continued*

Country	Rank	IMF	Rank	WB	Rank	CIA
Ecuador	88	7,195	73	7,397	93	7,200
Dominican Republic	89	7,041	90	5,334	95	7,000
Ukraine	91	6,941	76	6,916	96	6,900
Colombia	92	6,724	75	6,958	97	6,700
People's Republic of China	99	5,292	88	5,345	105	5,300
Jordan	105	4,886	94	4,903	112	4,900
Indonesia	120	3,725	104	3,728	127	3,700
Philippines	122	3,378	108	3,410	131	3,400
India	126	2,659	114	2,753	136	2,700
Pakistan	128	2,592	118	2,525	138	2,600

References

[1] Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. Lancet 2005:237–48.
[2] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd ed. Washington, DC: American Psychiatric Association; 1980.
[3] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd ed. Washington, DC: American Psychiatric Association; 1987.
[4] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington DC: American Psychiatric Association; 2000.
[5] Bramer GR. International statistical classification of diseases and related health problems. Tenth revision. World Health Statistics Quarterly 1988;41:32–6.
[6] Swanson JM, Sergeant JA, Taylor E, Sonuga-Barke EJ, Jensen PS, Cantwell DP. Attention-deficit hyperactivity disorder and hyperkinetic disorder. Lancet 1998;351:429–33.
[7] Tripp G, Luk SL, Schaughency EA, Singh R, DSM-IV, ICD-10: a comparison of the correlates of ADHD and hyperkinetic disorder. Journal of American Academy of Child and Adolescent Psychiatry 1999;38:156–64.
[8] Faraone SV, Sergeant J, Gillberg C, Biederman J. The worldwide prevalence of ADHD: is it an American condition? World Psychiatry 2003;2:104–13.
[9] Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. American Journal of Psychiatry 2007;164:942–8.
[10] Dubois RW, Chawla AJ, Neslusan CA, Smith MW, Wade S. Explaining drug spending trends: does perception match reality? Health Affairs (Millwood) 2000;19:231–9.
[11] Berndt ER. Pharmaceuticals in U.S. health care: determinants of quantity and price. Journal of Economic Perspectives 2002;16: 45–66.
[12] Berndt ER. The U.S. pharmaceutical industry: why major growth in times of cost containment? Health Affairs (Millwood) 2001;20:100–14.
[13] Scheffler RM, Hinshaw SP, Modrek S, Levine P. The global market for ADHD medications. Health Affairs (Millwood) 2007;26: 450–7.
[14] Addis A, Magrini N. New approaches to analysing prescription data and to transfer pharmacoepidemiological and evidence-based reports to prescribers. Pharmacoepidemiology and Drug Safety 2002;11:721–6.
[15] Rey JM, Sawyer MG. Are psychostimulant drugs being used appropriately to treat child and adolescent disorders? The British Journal of Psychiatry 2003;182:284–6.
[16] Hu TW, Bai J, Shi S. Household expenditure patterns in Tianjin, 1982 and 1984. The China Quarterly 1987:179–95.
[17] Biederman J, Faraone SV. Attention deficit hyperactivity disorder: a worldwide concern. The Journal of Nervous and Mental Disease 2004;192:453–4.
[18] Prendergast M, Taylor E, Rapoport JL, Bartko J, Donnelly M, Zametkin A, et al. The diagnosis of childhood hyperactivity. A U.S.–U.K. cross-national study of DSM-III and ICD-9. Journal of Child Psychology and Psychiatry 1988;29:289–300.
[19] Rousseau C, Measham T, Bathiche-Suidan M. DSM IV, culture and child psychiatry. Journal of the Canadian Academy of Child and Adolescent Psychiatry 2008;17:69–75.
[20] Clinical practice guideline: treatment of the school-aged child with attention-deficit/hyperactivity disorder. Pediatrics 2001; 108:1033–44.
[21] National Institute for Clinical Excellence Guidance on the Use of Methylphenidate (Ritalin, Equasym) for Attention Deficit/Hyperactivity Disorder (ADHD) in Childhood. Technology Appraisal Guidance, 2000 no. 13. http://www.nice.org.uk/cat.asp?c=11652; 2006 [accessed 19.12.06].
[22] Huskamp HA, Deverka PA, Epstein AM, Epstein RS, McGuigan KA, Muriel AC, et al. Impact of 3-tier formularies on drug treatment of attention-deficit/hyperactivity disorder in children. Archives of General Psychiatry 2005;62:435–41.
[23] Stein MA. Innovations in attention-deficit/hyperactivity disorder pharmacotherapy: long-acting stimulant and nonstimulant treatments. The American Journal of Managed Care 2004;10:S89–98.
[24] DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. Journal of Health Economics 2003;22:151–85.
[25] Off. USGA. Prescription drugs: companies typically charge more in the United States than in Canada. Comm. Energy Commer., House Represent. GAO/HRD-92-110. Washington, DC: Report to the Chairman, Subcommittee Health Environ; 1992.
[26] Frank RG. Prescription-drug prices. The New England Journal of Medicine 2004;351:1375–7.
[27] Xu B, Chiang EP. Trade, patients and international technology diffusion. Journal of International Trade and Economic Development 2005;14:115–35.
[28] Danzon PM. Pharmaceutical price regulation: national policies versus global interests. Washington, DC: AEI Press; 1997.