Is there any evidence that regulating pharmaceutical prices negatively affects R&D or access to new medicines? A systematic literature review.

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ABSTRACT

The Canadian federal government will be implementing changes to the guidelines used by the Patented Medicines Prices Review Board (PMPRB) on January 1, 2021. The amendments aim at imposing stricter price controls for patented medicines marketed in Canada. In response to an opinion piece arguing that tightening price controls in Canada would keep life-saving new drugs out of the country, the Executive Director of the PMPRB stated that there is no evidence of a link between pricing, research and development, and access to medicines. The objective of this paper is to test the veracity of that statement. A systematic review of published academic studies from January 1995 to May 2020 was conducted using the following databases: Academic Search Complete, EconLit, JSTOR, PubMed and Web of Science. Additional searching was performed with the aid of Google Scholar. Only empirical studies performed on populations of developed countries were considered eligible. Reference lists of papers identified were screened to track additional relevant publications. A total of 921 studies were retrieved after the initial search. Out of this retrieval, 34 articles were found eligible based upon study design, outcome measures and inclusion criteria. Searching through the reference lists of the retrieved articles yielded 15 additional articles. A total of 49 studies were considered to have met the inclusion criteria and relevant to be included in this review. Forty-four of the 49 studies reviewed showed a significant negative relationship between drug price controls and investment in pharmaceutical R&D or access to innovative drugs. The claim that there is no link between price and R&D or access to medicines is not supported by the evidence from the scientific literature.

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INTRODUCTION

The Canadian Federal government is in the process of implementing regulatory changes to the Patented Medicines Prices Review Board (PMPRB), the quasi-judicial agency whose mission is to regulate prices for patented drugs marketed in Canada. The changes are designed to impose stricter price controls in order to force down drug prices.[i]

These changes were originally intended to go into force on July 1, 2020 but have been postponed until January 1, 2021.

Some analysts and commentators have warned the government about the potential hidden costs associated with such a regulatory reform, arguing that it could negatively affect the incentives of firms to pursue R&D investment and to launch their new products in Canada in a timely manner.[ii] However, these warnings seem to have been ignored. In response to an opinion piece arguing that tightening price controls in Canada would keep life-saving new drugs out of the country, the Executive Director of the PMPRB stated that "there is no evidence of a link between pricing, research and development, and access to medicines".[iii]

The objective of this paper is to systematically review the literature for any evidence that price regulation negatively affects pharmaceutical R&D and the availability of new drugs.

METHOD

A systematic review of published academic studies from January 1995 to May 2020 was conducted using the 5 following databases: Academic Search Complete, EconLit, JSTOR, PubMed and Web of Science. Additional searching was performed with the aid of Google Scholar. Reference lists of papers identified were screened to track additional relevant publications.

The main keywords searched were "price", "price controls", "price regulation", "price caps", "price ceilings", "external reference pricing", "international reference pricing", "profit controls", "research and development", "R&D", "pharmaceutical innovation", "innovative medicines", "new drugs", "drug launches", "time of launch", "time of entry", "time to listing", "delayed launch", "access to medicines", "available medicines".

Articles specifically aimed to measure the impact of price level or price regulation on research and development (R&D), pharmaceutical innovation and access to innovative medicines were considered eligible (direct evidence). Studies examining the impact of price or price controls on expected return, sales revenue or profitability in the pharmaceutical industry were also included (indirect evidence).

The definition of price regulation includes not only direct price ceilings, but also other cost-containment measures explicitly designed to lower drug prices, such as external reference pricing schemes or therapeutic reference pricing. Other measures, such as drug formularies or mandatory generic substitution, were considered valid if authors explicitly used them as proxy for price control mechanisms.

Studies evaluating the effects of price regulation on pharmaceutical expenditures, health outcomes, affordability or consumption were excluded. Only peer-reviewed studies published in academic journals were included. Only studies performed on populations of developed countries were considered eligible. Only empirical and simulation-based studies were included; theoretical studies and commentaries were excluded. No specification with regard to drug type or therapeutic areas was made. No restriction of time was introduced, although all relevant studies identified were published after 1995. Only studies published in English were

[i] Patented Medicines Price Review Board. PMPRB Guidelines 2019. Ottawa: Government of Canada. https://www.canada.ca/content/dam/pmprb-cepmb/documents/consultations/draft-guidelines/draft-guidelines-en.pdf

[ii] Law, Michael and Wayne Critchley, "Ottawa's Plan to Change Drug Price Regulations is not Good Policy", *Policy Options*, October 12, 2018; Globerman, Steven and Bacchus Barua, *Pharmaceutical Regulation, Innovation, and Access to New Drugs: An international Perspective*, Fraser Institute, January 24, 2019; Rawson, Nigel SB, "Fewer New Drug Approvals in Canada: Early Indications of Unintended Consequences from New Patented Medicines Regulations", *Canadian Health Policy*, March 23, 2020.

[iii] Douglas Clark, "Low prices won't keep new medicines out of Canada", *Financial Post*, March 20th, 2020.

considered for this review. Of all articles that were considered to be eligible, a hard copy was retrieved.

RESULTS

A total of 921 studies were retrieved after the initial search. Out of this retrieval, 34 articles were found eligible based upon study design, outcome measures and inclusion criteria. Searching through the reference lists of the retrieved articles yielded 15 additional articles. A total of 49 studies were considered to have met the inclusion criteria and relevant to be included in this review.

Impact of price level or price regulation on pharmaceutical R&D

Out of the 49 studies[iv] retrieved, 16 sought to evaluate the relationship between drug price (or price regulation) and research and development in the pharmaceutical industry (see Table 1).

10 studies showed a significant negative link between price control policies and pharmaceutical R&D spending.[1,14,16,18,20,22,25,26,39,49]

5 studies showed that drug prices have a significant positive relationship with R&D investment.[4,5,29,34,35]

1 study concluded that no relationship between price regulation and pharmaceutical R-D exists.[33]

Impact of price level or price regulation on access to new medicines

Overall, 27 studies among those retrieved aimed to examine the link between price (or price regulation) and access to new medicines (see Table 2).

21 of them showed a significant negative link between price regulation and access to new drugs (availability, time to launch, etc.).[2,3,6,7,8,9,12,16,17,18,19,27,28,30,32,36,37,38,44,45,48]

5 studies showed a significant positive relationship between price and availability of innovative medicines.[10,11,24,31,34]

4 studies were inconclusive, had mixed results or found no relationship between price and availability of new drugs.[15, 23,42,46]

Relationship between price regulation and revenue/profits and between revenue/profits and R&D

Out of the 49 studies gathered, 7 explored the relationship between drug price controls and revenue/profits and between revenue/profits and pharmaceutical R&D spending (see Tables 3 and 4).

3 studies found that price regulation has a negative impact on revenue/profits.[41,43,47]

1 study showed that price regulation has a negative effect on R&D investment and drug availability.[16]

2 studies showed that higher expected revenue/profits have a positive influence on R&D investments.[21,40]

1 study found that higher expected sales revenue entailed by market size expansion has a positive impact on the number of new drugs introduced in that market.[13]

The policy implication of these results is that declining potential revenues or profits in the pharmaceutical industry, as a result of price regulation in certain markets, will discourage firms to pursue R&D investment and introduce new medicines, all other factors held constant.

DISCUSSION AND CONCLUSION

The vast majority of the studies reviewed showed a significant negative relationship between drug price controls and investment in pharmaceutical R&D or access to innovative drugs. Only five of the 49 studies reviewed found that price controls have no effect on pharmaceutical R&D or the availability of new medicines.

Estimates of R&D elasticity with respect to real drug prices found in the literature range from 0.5 to 0.6. This implies that for every 10% increase (decrease) in real pharmaceutical prices R&D investment increases (decreases) by 5-6%.[18,31] Accordingly, a price control policy which had limited the rate of growth in

[iv] Totals may not sum to 49 because some of the studies referenced above examined the link between price level or price regulation on both R&D and availability of new medicines.

pharmaceutical prices in the US to the rate of inflation (from 1980 to 2001) would have resulted in a 30% drop in R&D investment over this time period.[18]

The literature review also revealed that cross-country differences in drug price regulation affect the location of pharmaceutical Foreign Direct Investment (FDI). Indeed, countries with drug price controls were shown to be less likely to attract FDI investment than countries without price controls. Implementing price cuts or freezes leads to a significant 21% reduction in the probability of investment, all other factors held constant.[25]

Furthermore, it was found that price controls tend to discourage entry of new innovative medicines. A 50% decrease in drug prices, holding disease incidence and severity constant, decreases drug development by approximately 25%, according to one study.[5] Other researchers have shown that cutting prices by 40–45% in the US would lead to between 50 and 60% fewer compounds moving into clinical trials.[1]

A group of economists showed that about 330-365 fewer new drugs – representing 38% of all new drugs marketed worldwide – would have been brought to market between 1980 and 2001 if a price control policy had limited the growth rate of drug prices in the US to the rate of inflation.[18] Another study estimated that adopting price controls in the US similar to that observed in the other OECD countries would reduce the flow of new drugs entering the market by almost 40%.[17]

According to Moreno et al. (2017), if VHA-style price controls were applied to the Medicare Part D program, such price controls would reduce the number of new drug introductions by between 11.2% (low impact scenario) and 24.9% (high impact scenario) in 2060 relative to the status quo.[32]

Several studies have shown that new drugs are launched much faster in countries that have health policy institutions that promote availability and diffusion of innovative medicines. Researchers have estimated that introducing price controls reduces the hazard of drug launch by between 15%[6] and 21%[27], and could delay drug launches by as much as 80%.[6]

A group of researchers showed that if price controls similar to what exist in the other OECD countries were implemented in the US, pharmaceutical firms would see their revenues fall immediately by 10%, then by 18.4% after 3 years and by a 21.3% after 6 years.[43] This would likely have a negative effect on R&D spending and future drug discovery.

This review has shown that there is a substantial amount of published evidence showing a negative relationship between price regulation and pharmaceutical R&D and the availability of new medicines.

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Table 1. Summary of impact of price and price regulation on pharmaceutical R&D.

INDICATOR	IMPACT ON R&D
PRICE LEVEL	Positive: [4], [5], [29], [34], [35] • A 50% decrease in drug prices, holding disease incidence and severity constant, decreases drug development by as much as 25%.[5] • Rewarding firms with more generous prices (though a pharmaceutical policy like the PPRS in the UK) encourage them to move R&D operations in the country.[34] • Pharmaceutical R&D is driven almost exclusively by the economic harm caused by diseases that are prevalent in the United States, where drug prices are higher.[4] • Higher price premium for successful innovation drives increased pharmaceutical R&D in areas corresponding to unmet therapeutic needs and unexploited biological mechanism.[35] Negative: no study retrieved. Inconclusive/no significant impact: no study retrieved.
PRICE REGULATION	Positive: no study retrieved. Negative: [1], [14], [16], [18], [20], [22], [25], [26], [39], [49] • For every 10% increase (decrease) in real pharmaceutical prices in the US R&D investment increases (decreases) by 5.83%.[18] • Cutting prices by 40–45% in the US would lead to between 50 and 60% fewer compounds moving into clinical trials.[1] • R&D intensity by a pharmaceutical company positively correlates to its sales in the U.S market, and inversely correlates to the share of sales generated in the price-regulated European market.[14] • Implementing price cuts or freezes leads to a significant 21% reduction in the probability of pharmaceutical investment, all other factors held constant.[25] • Price-control threats in the US (1992-1993) have led to a decrease of cumulative R&D investment amounting to $7 billion for the following 5 years (1994-1998).[26] • Pharmaceutical R&D expenditures would have been between $251 and $256 billion (in 2000 US$) larger from 1962 to 2001 if the federal government's indirect controls had not negatively affected the real growth in drug prices.[39] • If prices in the US were regulated in a manner that resulted in pre-tax pharmaceutical profit margins in the US falling, on average, to the level observed in non-US markets, R&D would decline by about 25–33%, ceteris paribus.[49] • A national drug formulary, aimed at lowering drug prices, has a direct negative impact on R&D investments.[22] Inconclusive/no significant impact: [33] • Reference pricing did not negatively affect pharmaceutical R&D in British Columbia.[33]

Table 2. Summary of impact of price and price regulation on access to new medicines.

INDICATOR	IMPACT ON ACCESS TO MEDICINES
PRICE LEVEL	Positive: [10], [11], [24], [31], [34] • Countries with lower expected prices have fewer launches and longer launch delays, controlling for per capita income and other firm characteristics.[11] • New medicines tend to be introduced faster and have more intensive use in the US, where prices are higher.[24] • A 10% drop in drug prices entails a 5–6% decline in the number of distinct chemotherapy regimens treating a cancer site in the long run.[31] • Rewarding firms with more generous prices (though a pharmaceutical policy) encourage quicker diffusion of new and more innovative drugs.[34] Negative: no study retrieved. Inconclusive/no significant impact: [15], [23], [42] • Expected prices are correlated with a shorter time to launch in Belgium and Sweden, while they correlate with a longer time to launch in Scotland.[15] • Relatively high prices in Japan is not associated with faster submission of applications for drug registration.[23] • Drug price differences don't explain the longer submission delays for regulatory approval in Canada compared to that in the US and the EU, as expected first-in-class drugs don't have longer submission delays than follow-on drugs.[42]
PRICE REGULATION	Positive: no study retrieved. Negative: [2], [3], [6], [7], [8], [9], [12], [16], [17], [18], [19], [27], [28], [30], [32], [36], [37], [38], [44], [45], [48] • Countries with lower expected prices – due to cost-containment measures and regulation – have fewer drug launches and longer launch delays.[12] • Therapeutic reference pricing systems[9] and international reference pricing schemes tend to discourage drug launch and delay the adoption of new innovative medicines.[3,7,8] • Introducing price controls reduces the hazard of drug launch by between 15%[6] and 21%[27], and could delay drug launches by as much as 80%.[6] • If a price control policy had limited the growth rate of drug prices in the US to the rate of inflation from 1980-2001, about 38% fewer new drugs would have been brought to market.[18] • Adopting price controls in the US similar to that seen in the other OECD countries would reduce the flow of new drugs entering the market by almost 40%.[17] • If VHA-style price controls were applied to the Medicare Part D program, new marketed drugs could fell by between 11.2% and 24.9% in 2060.[32] • Price controls reduce the availability of the highest quality drugs.[2] Inconclusive/no significant impact: [46] • The fastest launch occurs when the launch price is moderately high, partly because health regulators behave strategically, trying to delay as much as possible new drug introductions with a high price tag.[46]

Table 3. Summary of impact of revenue/profit and profit regulation on pharmaceutical R&D.

INDICATOR	IMPACT ON R&D
REVENUE/PROFITS	Positive: [21], [40] • Pharmaceutical R&D expenditures have increased during the period 1974-1994 because major new drug introductions have generated favorable expected returns and important cash flows to finance new R&D projects.[21] • Profits create incentives to pursue R&D investments in order to bring new innovative drugs to market and generate additional profits in the future.[40] Negative: no study retrieved. Inconclusive/no significant impact: no study retrieved.
PROFIT REGULATION	Positive: no study retrieved. Negative: [16] • A 50% profit reduction, entailed by a cost-containment policy, would induce pharmaceutical firms to shut down over 85% of their R&D programs.[16] Inconclusive/no significant impact: no study retrieved.

Table 4. Summary of impact of revenue/profit and profit regulation on access to new medicines.

INDICATOR	IMPACT ON ACCESS TO MEDICINES
REVENUE/PROFITS	Positive: [13] • A revenue increase from market size expansion by 10% stimulate a 2.3% increase in the number of new chemical entities to respond to needs in that market.[13] Negative: no study retrieved. Inconclusive/no significant impact: no study retrieved.
PROFIT REGULATION	Positive: no study retrieved. Negative: [16] • A 50% profit reduction could lead to 85% fewer new drugs eventually entering the market.[16] Inconclusive/no significant impact: no study retrieved.