Research Paper

Drug Approval in India Does not Match the Disease Burden: A Cross-sectional Study

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Abstract

Objectives: To assess the correlation between drug approval and disease burden in India. **Materials and Methods:** A cross sectional study was conducted and data on drug approval for the past 14 years (2000–2013) were downloaded from the central drug standard control organization website in India and the latest data on disease burden from the year 2012 were obtained the World Health Organization website. Mortality and disability (disease adjusted life year) were considered. Drug approval was correlated with disease burden using the Spearman's correlation test. **Results:** Between 2000 and 2013, a total of 1913 drugs were approved in India. Of these, 838 were fixed-dose combinations and 22 were veterinary drugs, which were excluded from the analysis. Due to a single-drug being used for multiple indications, the final analysis was performed on 1345 indications/drugs. Overall, there was a weak correlation between disease burden and drug approval for the outcomes of mortality ($r = 0.207$, $P = 0.038$) and disability ($r = 0.278$, $P = 0.002$). **Conclusion:** The results from this first study assessing the correlation between drug approval and disease burden in India shows a significant mismatch and the urgent need for syncing the research output with the disease burden.

Keywords: Drug approval, disease-adjusted life years, disease burden, India

Introduction

Medical research has contributed significantly to the overall reduction in disease-related morbidity and mortality globally.[1] As a result, several diseases that contributed substantially to high mortality in the past are either no more or less life-threatening, as new measures to prevent or treat such diseases have been introduced. For example, between 1950 and 1990 the average life expectancy of people living in developing countries increased from 40 to 63 years mainly as result of innovations in the field of medical research. While the overall life expectancy has increased globally, the gap between developed and developing countries has remained significant.[2]

In recent years, there has been a significant trend in terms of medical research organizations shifting their base from developed countries toward developing countries. Specifically, India has become an attractive destination for development and testing of new drugs by pharmaceutical companies. Between 2004 and 2009, there was a 31% compounded annual growth rate in the clinical trial market in India.[3]

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While the increase in investment toward research efforts is laudable, it is unclear whether these added research resources are allocated toward the appropriate causes. We pose that research efforts and research funding in any country should focus on most prevalent diseases in that geographical area so that diseases responsible for relatively higher mortality and morbidity be given priority for research and funding.

To quantify such research efforts, drug approval serves as an important indicator. Our hypothesis is that there is a positive correlation between drug approval and disease burden for a given country and that no significant mismatch exists.

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Previously published studies assessing the association between drug approval and disease burden showed that such a mismatch exists. A study performed in Brazil by Vidotti *et al*., to evaluate the correlation between disease burden and drug approval found that there was a significant mismatch between these two variables. Similarly, another study by Trouiller *et al*., assessing trends in drug approval over a period of 25 years showed that only 1.1% of new drugs were approved for tropical neglected diseases responsible for 12% of global burden of disease (GBD).[4] However, despite the increase in research activities in India with the second largest population in the world a systematic assessment of correlation between drug approval and disease burden has not been performed, which is important for several reasons. Most importantly, such assessment will help in quantifying and prioritizing the research efforts and align research efforts with diseases that have the highest morbidity and mortality. The objective of this study is to assess the association between drug approval and disease burden in India, which in recent years has become one of the major contributors to the global clinical trial system.

Materials and Methods

Study design

This was a cross-sectional study and was performed and reported as per the STROBE guidelines.[5]

Data collection and extraction

Drug approval

Information on drugs approved in India was obtained directly from the website of the Central Drug Standard Control Organization (CDSCO). CDSCO is the drug authority of India responsible for drug approval.[6] This authority works under the Ministry of Health and Family Welfare, Government of India. Data were extracted from the website using a standardized data extraction form. Information related to the drug name, drug category, year of drug approval, and drug indications were extracted. Only single drugs were included in the analysis. Fixed-dose combinations were excluded from the analysis. All disease indications for the single drug were extracted from the CDSCO website and reclassified as per the classification of the GBD.[7]

Measures of burden of disease

Information related to the disease burden of India was collected from the World Health Organization (WHO) website.[8] The latest data available for disease burden of India are from 2012. As per the standard method of the WHO, the disease burden is measured using the outcomes of mortality and disability (disease-adjusted life years [DALYs]). Data related to both these measures were obtained.

Data analysis

Descriptive statistics in the form of frequency and percentages were used for disease burden and approved drugs. Spearman correlation was used to assess the association between burden of disease and associated mortality and DALYs with approved drugs. Two-tailed $P < 0.05$ was considered as statistically significant. SPSS Statistics for Windows, Version 17.0. Chicago: SPSS Inc was used for analysis.

Results

Characteristics of approved drugs

Between years 2000 and 2013, a total of 1913 drugs were approved in India. Out of these 1913, 838 were fixed-dose combinations (FDCs) and 22 were veterinary drugs, which were excluded from the analysis. Additional 79 drugs were excluded from the analysis for the reasons illustrated in Figure 1 resulting in a total of 974 drugs with 1266 indication pairs being included in the final analysis. As shown in Supplementary Figure 1, the number of drugs approved per year varied between 25 in the year 2000 to 2017 in the year 2008.

Characteristics of disease burden of India

As per the WHO data, the major disease categories for mortality were cardiovascular diseases (29.5%), infectious and parasitic diseases (16.9%), respiratory diseases (14.5%), neonatal conditions (8.2%), and malignant neoplasms (7.9%). Major disease categories for disability were infectious and parasitic diseases (13.53%), musculoskeletal diseases (12.27%), digestive diseases (10.41%), malignant neoplasms (8.85%), and cardiovascular diseases (7.66%).

Comparison of burden of disease and approved drugs

Outcome: Mortality

The top 20 diseases associated with the highest mortality and the drugs approved for these conditions are shown in Figure 2. Briefly, the top 10 diseases associated with highest mortality were ischemic heart disease (14.1%), chronic obstructive pulmonary disease (12.3%), stroke (10.2%), diarrheal disease (6.8%), lower respiratory infections (5.6%), preterm birth complications (4.4%), tuberculosis (3.1%), diabetes mellitus (2.6%), cirrhosis of the liver (2.5%), and kidney diseases (2.4%). However, only 1.7% of drugs were

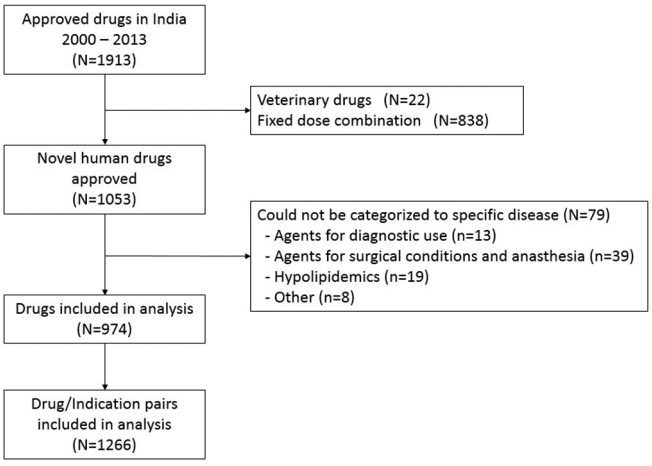

Figure 1: Flow chart diagram regarding the selection of drugs for the analysis

approved for ischemic heart disease (14% mortality), 1.3% for chronic obstructive pulmonary disease (12.3% mortality), 0.4% for stroke (10.2% mortality), 1.0% each for diarrheal disease (6.8% mortality) and lower respiratory infections (5.6% mortality), 0.2% for preterm birth complications (4.4% mortality), 0.1%for tuberculosis (3.1% mortality), 1.9% for diabetes mellitus (2.6% mortality), 0.6% for cirrhosis of the liver (2.5% mortality), and 0.6% for kidney diseases (2.4% mortality) [Figure 2]. Overall, 64% of deaths were attributable to the above mentioned 10 diseases while only 8.8% of approved drugs were developed for these diseases. While statistically significant, the overall correlation between causes of mortality and drug approved for each cause was weak ($r = 0.207$, $P = 0.038$).

Outcome: Disability

The top 20 diseases associated with the highest disability and the drugs approved for these conditions are shown in Figure 3. In short, the top 10 diseases associated with highest disabilities were preterm birth complications (7.5%), ischemic heart disease (7.1%), chronic obstructive pulmonary disease (7%), diarrheal diseases (6.3%), lower respiratory infections (5.6%), stroke (4.6%), birth asphyxia/birth trauma (3.4%), iron-deficiency anemia (3.1%), sense organ diseases (2.9%), and unipolar depressive disorders (2.6%). However only 0.2% of drugs were approved for preterm birth complications (7.5% mortality), 1.7% for ischemic heart disease (7.1% disability), 1.3% for chronic obstructive pulmonary disease (7% disability), 1% for diarrheal diseases (6.3% disability), 1% for lower respiratory infections (5.6% disability), 0.4% for stroke (4.6% disability), 0% for birth asphyxia/birth trauma (3.4% disability), 0.1% for iron-deficiency anemia (3.1% disability), 3.6% for sense organ diseases (2.9% disability), and 1.7% for unipolar depressive disorders (2.6% disability) [Figure 3]. Overall, these top 10 diseases were associated with 50% of total DALYs while only 11% of approved drugs were targeting these diseases. There was a statistically

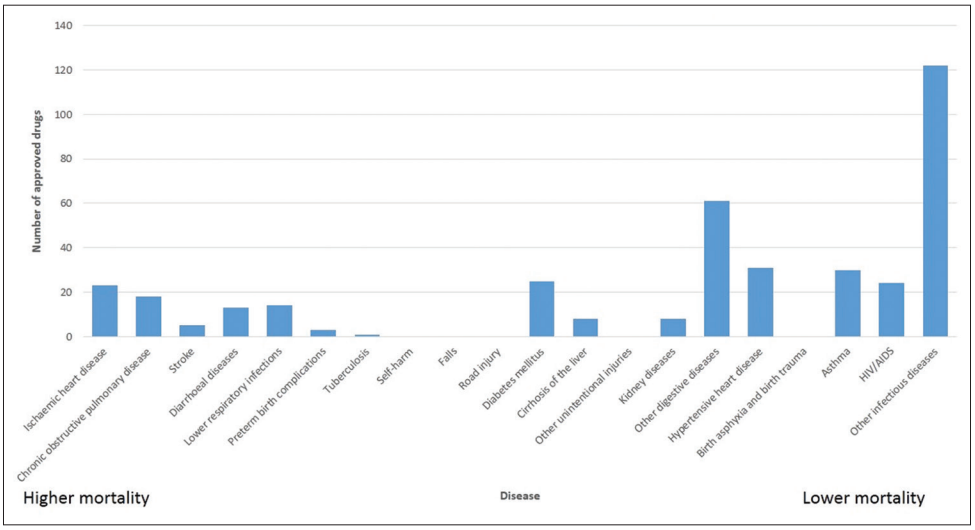

Figure 2: Number of new drugs approved for top twenty causes of mortality in India

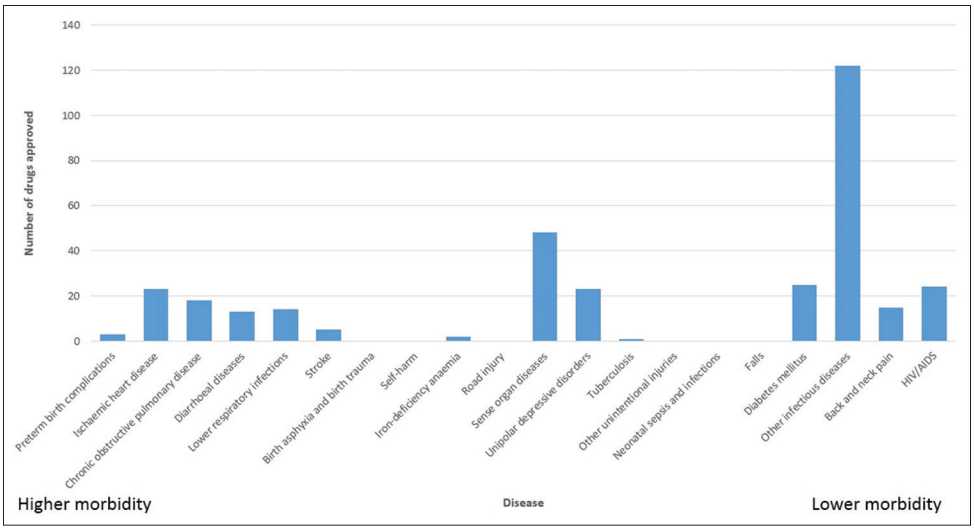

Figure 3: Number of new drugs approved for top twenty causes of morbidity in India

significant weak correlation between causes of DALYs and drugs approved for these conditions ($r = 0.278$, $P = 0.002$).

Discussion

To the best of our knowledge, this is the first study assessing the correlation between drug approval and disease burden in India. The results show a weak correlation between drug approval and disease burden as indicated by mortality and disability. That is, the majority of approved drugs in India are not for conditions associated with the highest disease burden.

The findings of this study are not entirely surprising, and the reasons behind these results may be multifactorial. First, majority of medical research globally is conducted by pharmaceutical companies. Given that, pharmaceuticals industry is a for-profit business, their focus is on the payers who have the purchasing capacity for drugs concerning the indication prevalent in a specific country (i.e., developed countries). Accordingly, even with a shift in clinical trials enterprise to a country like India, the priority market is still the developed world.[9] This trend is also evident from similar studies conducted in developed countries which reported a significant association between new drug approval and disease burden.[10] That is, despite the availability of workforce and a large pool of patients, clinical trials in India are conducted by international pharmaceutical companies, which explore mainly interventions for diseases which are common in developed countries.[11]

There are also possible noneconomic factors associated with this mismatch in drug approval and disease burden. For instance, the drug approval process requires a system linking the research cycle from bench to bedside which is either nonexistent or, even if it exists, is mired in bureaucratic hurdles.[12] The absence of such a system leads to a shortage of qualified professionals to guide the research enterprise in India. Pharmaceutical companies or the government, which is involved in the drug development, require qualified personnel to undertake such research becomes an uphill task given the shortage of qualified professionals. On that note, approximately 5900 doctoral degrees are awarded annually in India in the field of science and technology.[13] However, this is minuscule given the total population of India which stands at 1.3 billion. In contrast, the United States of America, which has a significantly smaller population, produces four times more Ph.D. graduates annually.[13] Coupled with reductions in overall spending for research and innovation, the whole system of research cycle required for drug development is compromised. In short, there is an urgent requirement to streamline the system for drug development and approval and focus on the development of professionals to address the shortage of qualified human capital.

We did not find any similar study assessing the correlation between drug approval and disease burden in India. However, there are similar studies specifically in the field of neglected tropical diseases which also concluded that there is a need for research to address diseases that affect people living in the developing world.[4] Another study by Catalá-López *et al*. also evaluated the association between new drug approval and disease burden found a high correlation between drug approval and DALY for developed countries, but the correlation was moderate for low- and middle-income countries.[10] The study by Vidotti *et al*. conducted in Brazil also concluded that there is a mismatch between drug approval and disease burden.[14]

The study also has some limitations. One of the key limitations is the inclusion of only new drugs and exclusion of the FDCs. Nevertheless, it is important to note that majority of fixed-dose combinations include single agents already in use for a specific disease/s and the aim of the combination is to increase efficacy or for pharmacokinetic considerations and not necessarily represent a new drug in entirety. Another limitation includes the time limit of years 2000–2013 and it is possible that innovations before that era may have been missed. However, given that, research efforts are still in its infancy in India, it is very unlikely that results would be impacted in any way due to the time span of the past 14 years. For example, the number of drugs varied across years of approval with a low of 25 drugs in the year 2000, high of 217 in the year 2008 and in the year 2013, the number of the approved drug was 25 as well. Therefore, given the time span of 14 years, it is highly unlikely that trend has changed significantly.

Conclusion

The findings from this study highlight an important issue of mismatch between drug approval and disease burden in India. The results show that there is an urgent need for escalating the research output to address the GBD.

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Conflicts of interest

There are no conflicts of interest.

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