Evaluation of the Development of R&D into Parkinson’s Disease through Technology Monitoring Using Patent Documents and Scientific Articles

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ABSTRACT
Characterized as a progressive neurodegenerative disease caused by the loss of dopaminergic neurons in the substantia nigra, Parkinson’s disease is affecting an ever greater number of people around the world as global life expectancy rises. As the disease progresses, it has physical, mental, emotional, social, and economic impacts on the patient, eroding their quality of life. Many studies have been done to understand what leads to the onset of the disease and to develop treatments or even prevention. This study uses technology foresight by identifying patents and scientific articles related to drugs for the treatment of the disease with the purpose of assessing the progress of research over time and map out the countries and companies that control the related technologies.

Keywords: Parkinson’s disease, Drugs, Population aging, Patents

INTRODUCTION
The population of the world is aging rapidly. As average global life expectancy rises (see Figure 1), diseases previously considered rare have started to become an increasing concern. This rapid, ongoing change in the world scenario indicates that an increasingly higher number of old people are likely to be diagnosed with neurodegenerative diseases. With a prevalence of approximately one case in every 300 people [1], these diseases cause the progressive degeneration and death of nerve cells, impairing brain function and triggering the onset of dementia. The diseases grouped under this title include Alzheimer’s, Parkinson’s, Creutzfeld-Jacob, and Huntington’s [2].

Statistical data show that the number of people over 60 years of age is on the rise throughout the world. Unless a prevention or cure for Parkinson’s disease (PD) is found, the number of people suffering from it will grow substantially in the coming years. According to Dorsey et al [4], the
number of people with PD in the ten most highly populated countries in the world and the five largest in western Europe – which stood at around four million in 2005 – could reach as many as nine million by 2030 (see Figure 2).

Parkinson’s disease is the second most common neurodegenerative disease, and affects approximately 1% of individuals over 50 years of age and 2.6% of people aged 85 or over. Onset tends to occur in the 58-60 age group, but cases of early onset amongst people in their 40s or even their 30s have been reported, with a higher incidence amongst men than women, at a proportion of 3 to 2 [5].

Figure 2. Estimated number of individuals with Parkinson’s disease from 2005 to 2030 [4]

In view of the prospects for the increased prevalence of PD around the world, researchers are keen to discover more effective drugs to prevent, treat or even cure people with it. Many medicines already exist, but despite the pharmacological progress made, PD still remains an incurable, progressive pathology, and a considerable challenge for researchers. It is important to stress that there is as yet no standard treatment regimen for the disease, either using a single drug or a combination of drugs, capable of guaranteeing convincing, sustainable benefits. Furthermore, the treatments that do exist do not seem to halt or reverse the neurodegenerative process [6]. The cost of treating these patients goes up as the disease progresses and often exceeds the means of the families, putting more physical and emotional strain on everyone involved. The socioeconomic impact will be a major challenge in the future, because the incidence of the disease will grow as the population ages, becoming a major public health problem.

Parkinson’s disease

Parkinson’s disease (PD) is a neurodegenerative disease that mainly affects the motor system. The most common symptoms are tremors, muscle rigidity, akinesia, and postural instability. However, non-motor manifestations can also occur, like memory lapses, depression, sleep disturbance, and impairment of the autonomic nervous system [7]. The clinical signs of PD were first described in 1817 by a British physician called James Parkinson in his classic text, “An Essay on the Shaking Palsy” [8,9], but it was only in 1920 that Jean-Martin Charcot recognized the pioneering nature of Parkinson’s description of shaking palsy, naming it after the person responsible for its discovery [10,11].

It is still not clear exactly what mechanisms trigger the onset of Parkinson’s disease, but it is known that aggregates of protein, especially alpha synuclein, in the form of intracellular fibrils (Lewy bodies), are directly associated with the development of the disease [8]. These protein inclusions, which are toxic, aggregate in neurons, causing their death and the loss of dopaminergic neurons present in the substantia nigra.

Although its cause has not been discovered, it is known that Parkinson’s disease causes the loss of at least 50% of the cells in the substantia nigra, bringing about an 80% reduction in the amount of dopamine that reaches the striatum [12]. Trembling in the hands and fingers is called resting tremor, because it happens when the patient is not making any movement. Muscle rigidity can affect different parts of the body, and people with the disease take longer to do simple motor tasks like getting dressed, cooking, or writing.

The disease affects an age group associated with high comorbidity rates. The first symptoms appear when around 60% of the dopaminergic neurons in the brain have already been impaired, which makes diagnosis hard. The mechanisms involved in the production of the protein aggregates implicated in the
onset of the disease have been studied by different research groups to find a method of preventing their formation or even eliminating them from patients already with the disease [13].

Today, the main treatments involve the use of drugs such as levodopa, carbidopa, and pramipexole. Some studies into the use of carboxylic compounds are being done, as these compounds slow down the dopamine oxidation process, which is understood to be one of the main factors behind the progress of the disease [14,15].

The purpose of this study is to use technology foresight techniques to present an overview of the latest scientific and technological developments for Parkinson’s disease and identify the main actors and leading countries in the sector, by conducting a scientific literature review and patent analysis.

**METHODOLOGY**

Evaluating scientific production is extremely important for identifying and analyzing new or, indeed, consolidated areas of research, and an excellent indicator for public policymaking and funding allocation. The review of the scientific literature done for this study consisted of associating terms related to Parkinson’s disease. The words searched in combination to identify studies of interest were: “Parkinson” and “substantia nigra” and “alpha synuclein” or “Lewy bodies”. The Web of Science¹ database was used, and the timeframe covered went from 1995 to 2012. Only complete articles and review articles were separated, resulting in a total of 17,510 documents retrieved, which were saved and exported to VantagePoint®, a software package suitable for processing large quantities of data. Once repetitions had been excluded, a new search was done to identify only those articles that contained the terms “drug” or “medicine” in the title or abstract, because the focus of this study was to analyze research into drugs and medicines for Parkinson’s disease. This process resulted in the identification of 1,621 articles.

The patent analysis was done using the Derwent Innovations Index database, which we accessed via the Capes portal. It was picked for this purpose because it is internationally recognized and contains over 11 million patent documents filed, published, and sometimes granted in over 40 countries since 1963 [16].

The search strategy used the same timeframe as the scientific articles, and crossed the Parkinson’s keywords and drug with International Patent Classification² code A61P- 025/16 (Anti-Parkinson Drugs). A total of 2,731 documents were encountered for the period in question.

**RESULTS AND DISCUSSION**

The analysis of scientific articles is an important tool for identifying specialists, and mapping out institutions, collaborations, and countries investing in the subject, giving a better understanding of the knowledge creation process in this area. Our search of scientific articles into drugs for Parkinson’s disease (PD) clearly demonstrates how academic interest in the subject has grown over the years (Figure 3). This increase is in line with the significant rise in the number of cases of the disease, prompting research institutions to study the mechanisms involved in the loss of dopaminergic neurons with a view to obtaining an effective treatment.

![Figure 3](image-url)

Figure 3. Evolution of the number of scientific articles during the time period studied

¹Web of Science is available at federal institutions in Brazil via the Capes portal.

²The International Patent Classification (IPC) is used to classify technical content in patent documents, dividing technology into eight sections that help when documents are being retrieved for analyses of this kind.
The institutions that have published most papers about drugs for PD treatment are from the United States (Figure 4). The country of origin of the papers was designated according to the country of origin of the lead author. Accounting for around 30% of all the scientific articles on the subject, the U.S. is the clear leader in the production of knowledge on PD. The studies seek to understand the processes that lead to the onset of the disease with the aim of encountering mechanisms to develop more effective drugs with fewer side-effects than the ones currently on the market. This interest reflects the fact that in the United States there are now more than one million people with the disease, and 60,000 new patients are diagnosed every year.

Eight of the ten institutions that have published most articles on the subject are universities (Figure 5), with Harvard taking the lead. Indeed, Harvard University has a pioneering biomedical research group investigating the nervous system – the Harvard Neuro Discovery Center – with a highly qualified team of researchers devoted to speeding up the discovery of effective treatments and cures for neurodegenerative diseases [17]. Their published studies report on investigations of mechanisms that may influence the development of the disease or halt the neurodegenerative process.

Patent Documents

Patent documents are important sources of technological information, giving a picture of the stage of development of new technologies and their impact on society, and thereby supplying inputs for strategic planning and decision making by public and private institutions. They are one of the main tools used for mapping out what direction technology development is headed.

The historical profile of patent applications can be seen in Figure 6, based on their priority date. A significant increase in the number of patent applications filed can be seen over the years. The reason for this could be that the number of people with PD is on the rise the world over. The authors of a

3 The priority date is the date the first application is filed in the country of origin.
study called "Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030" indicate the imminent problem of the aging of the population, suggesting that the number of people with PD will almost double by 2030 [4]. Research into PD, the most widespread disease that impairs motor function, focuses on finding improved pharmacological treatments. Surgery has also been investigated by many neuroscientists with a view to diminishing the costs and improving the techniques, but the most promising area at the present time is stem cell therapy [18]. In PD, there is a relatively selective loss of dopaminergic neurons in a specific area of the brain [19], and as pharmacological treatments and surgery are only able to alleviate symptoms but cannot halt the progression of the disease, many studies have pointed to the potential impact of creating dopamine-producing cells from stem cells, which could introduce new approaches to the treatment of the disease [20]. Over the years, great progress has been made in understanding the mechanisms involved in the dysfunctions of the central nervous system [21]. Even so, many drugs have not passed the clinical trial stage or not been developed into final products because of the strength of their side effects. This has a severe financial impact both on drug companies, because of the years this kind of research and development takes, and on society, which keenly awaits new breakthroughs in the treatment of the disease. These costs could be one reason for the fall-off in the number of patent applications filed in recent years (see Figure 6). However, another important factor could be the peculiarity of the patent system, whereby patent applications are held in confidence for 18 months after filing, not to mention the time taken for patent applications to be indexed in databases.

When we analysed the profile of patenting in this area from the perspective of the countries in which priority applications are filed, we found that 51% of them were filed in the United States (Figure 7). This country’s absolute leadership of the production of scientific publications and filing of patent applications is indicative of its interest in finding treatments to alleviate the socioeconomic impacts of the disease, whose direct and indirect cost has been estimated at around 27 billion dollars a year, including treatment, social security payments, and loss of income because of incapacity to work [22].
At the same time, the pharmaceutical industry is keen to harness the commercial potential of this disease, which, with no known cure, a global footprint, and patients who require treatment on a daily basis for the rest of their lives after diagnosis, represents a huge potential source of revenue.

The prospect of earning sustainable profits on a global scale is what drives the drug companies to invest in the research and development of new products for diseases like Parkinson’s, rather than tropical diseases, for instance, which are mostly restricted to poor and developing countries, significantly reducing the expectations of returns on invested capital.

It is important to note the pharmaceutical industry’s interest in seeking patent protection in Asian countries, which is a promising market, as the number of people with PD in these countries is set to rise from 2.57 million in 2005 to 6.17 million by 2030 [23].

Figure 8 shows the top assignees of patents for PD. Companies that had filed at least 50 applications in the area were selected. Most are from the U.S., once again demonstrating the country’s dominance of the technology used to develop drugs for PD. Give that this is a progressive disease for which there is no cure, and which can result in severe disability, its social and financial impacts are high. Antiparkinson drugs are expensive for early-stage patients, but are four times as expensive for patients at an advanced stage of the disease [24]. The search for new drugs is of great interest to the industry, which is keen to invest in the development of new products that outperform existing options on the market, since if they are able to launch a new product, they will be assured financial returns far beyond the 20-year monopoly assured by the patent. Leaders in the sector, American drug companies are the ones that have invested most in innovation and are therefore the ones that have posted the highest profits from this lucrative market. U.S. companies currently account for 52.9% of global drug sales [25].

The company with the most patents in this area is Pfizer (Figure 9). It is the world’s biggest pharmaceutical company, and with its acquisition of Wyeth in 2009 it consolidated its position as a top patent holder and a leader in the market for the treatment of diseases affecting the central nervous system, pain and inflammation, and cardiology. Pfizer’s activities in the treatment of Parkinson’s disease are coordinated by Pfizer Neuroscience, which has an integrated team of professionals who work together to identify novel drug targets and advance them into clinical testing with the aim of launching novel medications to treat diseases that affect the nervous system, including Parkinson’s disease [26]. The current trend in the pharmaceutical industry is to seek ways to halt the development of the disease at some point in the process, reducing the progression of symptoms and thereby guaranteeing sales and associated profits, because patients with the disease are always on the lookout for potential new drugs that give them hope of more effective treatment.
CONCLUSION

Scientists around the world are working towards developing new treatments with the capacity to retard or inhibit the degeneration of dopaminergic neurons, since there is not yet any medicine or treatment capable of blocking the advance and progression of the disease. The difficulty of finding cures, preventive methods or early diagnosis has prompted research centers and companies alike to invest heavily in researching Parkinson’s disease. The data in this article show that the number of studies into the disease has risen as the prevalence of the disease has increased. The results obtained reveal that the number of cases is set to rise quickly, and that more research funding may be needed for more significant progress to be made. Developed countries lead the field in the number of scientific publications produced and the number of patents held in the area, with the United States standing head and shoulders above all other countries. Driven by the rise in the number of Americans with PD and the chronic nature of the disease, pharmaceutical companies and institutions are investing in the quest for new drugs. Demographic data reveal that the number of people with PD is likely to rise in developing countries, too, where the lack of effective, secure, and economically feasible treatments could be a cause of suffering. This only goes to reinforce the need for the public and private sectors to make ever greater investments in research for Parkinson’s disease.

REFERENCES


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