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Emerging Growth of Orphan Drugs for Neurological Diseases in Japan: Potential Benefits for Both Patients and Pharmaceutical Companies

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Abstract

Despite the existence of numerous rare neurological diseases, no studies have been conducted on orphan drugs for neurological diseases available on the Japanese pharmaceutical market and their potential benefits. In this context, from a statistical perspective, we investigated 1) the market position of orphan drugs in Japan, and 2) the market penetration of generic medicines. To the best of our knowledge, this is the first empirical study to examine the current status and development strategy of orphan drugs approved for neurological diseases in the Japanese pharmaceutical market. The perspectives provided by this research are expected to promote the clinical development of orphan drugs in Japan for patients suffering from intractable neurological diseases that currently have no known effective therapies. The dataset used in this research was generated from publicly and commercially available data sources in Japan. Marketing approvals for orphan neurological products have increased dramatically in recent years. As much as 10% of all drugs approved for neurological diseases in Japan were orphan drugs that met urgent medical needs. Six of these orphan drugs were ranked in top 500 best-selling drugs in Japan, which indicated the presence of a potentially large market. Compared with more conventional drugs, the prices of orphan drugs are not expected to be reduced. In addition, due to an apparent lack of competition from generics, the quantity of available orphan drugs has remained steady, suggesting stable long-term sales. Most orphan drugs in Japan can adopt innovative marketing strategies that divide major neurological diseases into a more specific variety of rare disease categories. We found that orphan drugs approved for neurological diseases in Japan have been launched steadily. It is unlikely that these drugs will be affected by regular price revisions and the launch of their generic counterparts. Based on these findings, the further development of orphan drugs in Japan should be encouraged in order to meet urgent medical needs and deliver innovative drugs to patients suffering from rare neurological diseases.

Keywords:
drug development, neurology, orphan drug, Japanese pharmaceutical market, Pharmaceuticals and Medical Devices Agency (PMDA)

1. Introduction

Orphan drugs (OD) are pharmaceutical products for the treatment of very serious or life-threatening rare diseases. A rare disease is defined as one affecting less than 200,000 (about 1 in 1,500) and 50,000 (about 1 in 2,500) patients in the United States (US) and Japan, respectively[1]. Because orphan drugs are for treating rare diseases, and the target number of subjects enrolled into clinical trials is likely to be small, it may be falsely assumed that the development costs of orphan drugs are less than those of non-orphan drugs. Furthermore, the Japanese pharmaceutical industry has appeared to have little interest in developing drugs intended for only a small number of patients. This is likely because the extremely high cost associated with launching a product into the pharmaceutical market cannot be recovered through sales if the potential market is small, as is the case with products for treating rare diseases. Accordingly, drug companies may incur a financial loss by choosing to develop these drugs.

In addition, the diagnosis of orphan diseases is often time-consuming and difficult due to limited evidence from basic research and a lack of experience and knowledge regarding treatment among medical staff[2, 3]. Furthermore, the low number of patients with rare diseases leads to small sample sizes in clinical trials, making statistically significant data difficult to obtain[4]. Joppi et al[5]. reported that the success rates for orphan and non-orphan drug development were 62.9% and 70.7%, respectively, suggesting that the development of successful orphan drugs remains difficult.

Based on these findings, orphan drug development is associated with numerous challenges, including a low success rate,

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the small number of patients enrolled in clinical trials, and limited knowledge of the diseases themselves, which leads to difficulties in setting end points in clinical trials[6]. Therefore, pharmaceutical firms seeking to maximize profits have not historically invested fully in the research and development of orphan drugs[7]. Consequently, patients with rare diseases have typically been neglected and "orphaned".

There are regulatory differences in the number of patients necessary for being designated as orphan disease; fewer than 251,250 in EU, fewer than 200,000 or more 200,000 patients if the development cost will not be recovered in US, and fewer than 50,000 in Japan[8]. However, it has recently become clear that rare diseases actually provide a viable business opportunity[9] and many pharmaceutical companies have started to significantly invest in the research and development of orphan drugs. As a result, more than half of the orphan drug market share has been captured by the major global pharmaceutical companies[10]. What has spurred this drastic change?

The primary reason for this change was the enactment of new regulations for orphan drugs. The Orphan Drug Act (ODA) was enacted in the US in 1983 to stimulate orphan drug development. The ODA guarantees fiscal and regulatory incentives−including market exclusivity, tax credits, research and development grants, and pre-approvals−to pharmaceutical companies who develop orphan drugs[11]. Subsequently, Japan and many European countries enacted similar regulations[12]. The number of newly-launched drugs is considered to be a good indicator of the impact of these orphan drug-related regulations[13]. In the US, during the decade before the ODA, only 10 products obtained market approval[14]; however, after the ODA was enacted, orphan drugs accounted for around one-third of new molecular entities approved by the Food and Drug Administration[15], and a significant increase was observed in clinical trials for orphan drugs[16].

A previous study revealed that Japan's unique reward premium system, which sets high prices at drug launches, will likely apply to the orphan drugs developed for neurological diseases[17], and that the impact of this incentive system on the field of neuroscience would be substantial[18]. Moreover, the share of neurological drugs within the Japanese pharmaceutical market, which is less affected by generic penetration than other therapeutic areas such as cardiovascular drugs, has been increasing[19]. All in all, the current environment in Japan is facilitating the development of neurological drugs. It has already been reported that in the US, between 2006 and 2011, 17% of all orphan drug approvals were for neurological diseases, making it the second largest share of orphan drugs[20]. However, no empirical research from this perspective has been reported in Japan.

Japan is referred to as a "super-aging society" due to high life expectancies resulting from medical advancements[21]. Considering the effects of aging on the brain [22], an increasingly urgent medical need for neurological drugs is expected. However, several studies have noted that significant lags in drug development for neurological diseases still exist in Japan[23–25]. Therefore, many patients in Japan are unable to receive the global standard of care in neurology.

In this context, we investigated the orphan neurological products in Japan and the degree to which they provide benefits to both patients and pharmaceutical companies. To the best of our knowledge, this is the first comprehensive and empirical study to attempting to clarify the current market status of orphan drugs approved for neurological diseases, as well as the penetration of generic medicines in Japan. The perspectives provided by this article are expected to promote the development of orphan neurological products in Japan, which in turn is expected to improve the quality of life of patients suffering from intractable neurological diseases that currently have no known effective therapies.

2. Materials and Methods

2.1. Data sources

The dataset used in this research was generated from publicly and commercially available data from both the IMS Japan Pharmaceutical Market database and the *Manual of Therapeutic Agents 2015*[26]. The top 500 domestic pharmaceuticals in terms of quantity and sales between 2009 to 2014 were used. Data obtained from the IMS database on psychiatric drugs were excluded. In addition, as described below, the latest neurological products were extracted based on information in the *Manual of Therapeutic Agents 2015*, which is the guidebook most commonly used by Japanese clinical staff in medical practice. To create the drug price database, we utilized information from the website of the Japanese Ministry of Health, Labour and Welfare (http://www.mhlw.go.jp/english/).

2.2. Classification of neurological drugs

The neurological drugs selected were classified as follows based on the disorder they were developed to treat: Parkinson's disease; epilepsy; cerebrovascular disorder; muscular rigidity; myasthenia gravis; Alzheimer's disease; dizziness; multiple sclerosis; and other (Guillain-Barré syndrome, Huntington's disease, myoclonus, restless legs syndrome, amyotrophic lateral sclerosis (ALS), autonomic dysfunction, spinocerebellar degeneration, and secondary neurodegenerative insults). The launch dates of the selected neurological drugs were identified using publicly available information from the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) website (http://www.pmda.go.jp/english/).

2.3. Orphan drugs

Orphan drugs approved to treat neurological diseases were selected using publicly available information from both the National Institute of Biomedical Innovation (http://www.nibio.go.jp/english/index.html) and PMDA websites.

2.4. Statistical analysis

Simple linear regression model was performed to assess changes in the clinical use of riluzole (Rilutek), taltirelin (Ceredist), donepezil hydrochloride (Aricept), and edaravone (Radicut) between 2009 and 2014.

Fig. 1.

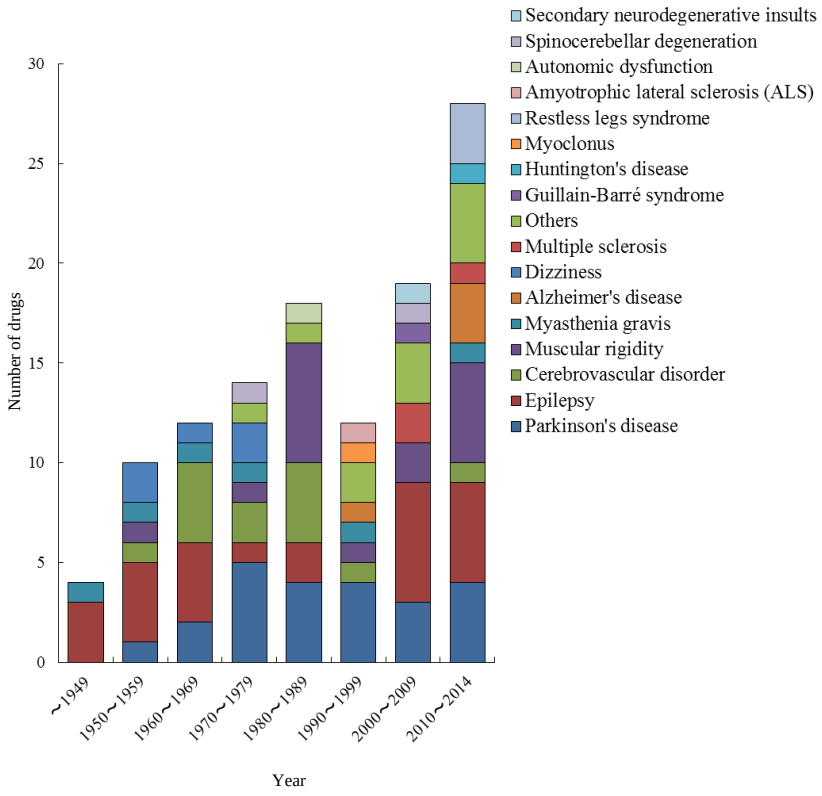

Figure 1: The number of neurological drugs approved in Japan by decade Drugs in the "other" category are as follows: autonomic dysfunction, amyotrophic lateral sclerosis (ALS), myoclonus, Guillain-Barré syndrome, spinocerebellar degeneration, secondary neurodegenerative insults, Huntington's disease, and restless legs syndrome

Table 1. Profiles of orphan drugs for neurological diseases ranked in the top 500 in sales in 2014

Brand name	Generic name	Indication	Rank	Approval year	Development strategy	Generic
Ceredist	Taltirelin	Spinocerebellar degeneration	117	2000	OD	Yes
Venoglobulin IH	Polyethylene Glycol Treated Human Normal Immunoglobulin	Myasthenia gravis	164	2011	Non-OD → OD	No
Kenketsu venilon-I	Freeze-Dried Sulfonated Human Normal Immunoglobulin	Guillain-Barré syndrome	203	2000	Non-OD → OD	No
Kenketu glovenin-I	Polyethylene Glycol Treated Human Normal Immunoglobulin	Myasthenia gravis	228	1999	Non-OD → OD	No
Rilutek	Riluzole	ALS	392	1998	OD	Yes
Betaferon	Interferon beta-1b	Multiple sclerosis	484	2000	OD	No

ALS: amyotrophic lateral sclerosis; OD: orphan drug.

Non-OD → OD: First indication was non-orphan disease. Second indication was orphan disease.

3. Results

Trends in the launch of the neurological drugs in Japan are shown in Figure 1. The number of available neurological drugs has been steadily increasing, which suggests that the promotion of neurological drug development in Japan has largely been successful. In addition, since 2010, "other" drugs for neurological diseases with urgent medical needs, most of which are designated as orphan diseases, have been launched steadily in Japan. The neurological drugs currently available in Japan clas-

Fig. 2.

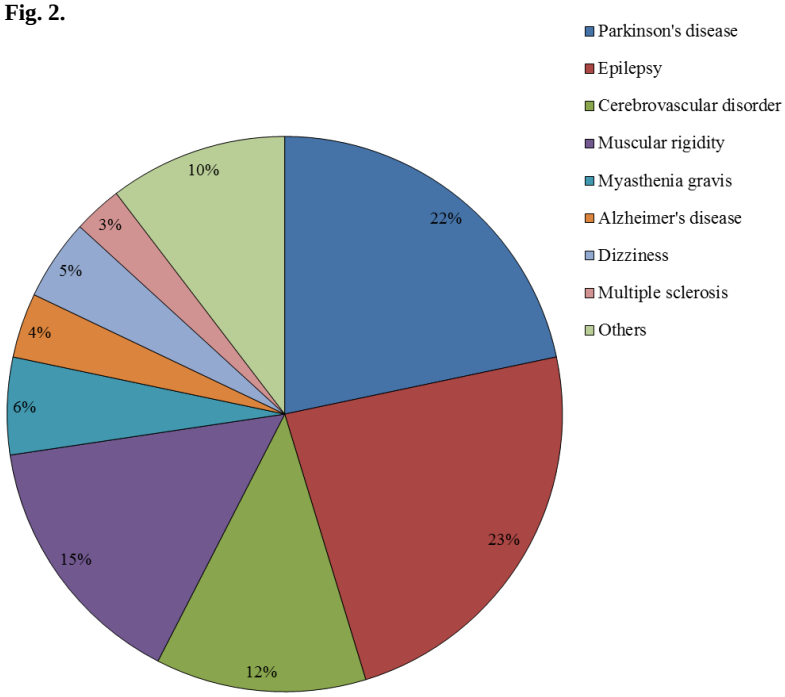

Figure 2: The proportion of neurological drugs presently approved in Japan Drugs in the "other" category are as follows: autonomic dysfunction, ALS, myoclonus, Guillain-Barré syndrome, spinocerebellar degeneration, secondary neurodegenerative insults, Huntington's disease, and restless legs syndrome

Table 2. Fluctuations in the prices of riluzole (Rilutek), taltirelin (Ceredist), donepezil hydrochloride (Aricept), and edaravone (Radicut)

	Drug price (yen)			Ratio			
Brand name	2010	2012	2014	2010/2008	2012/2010	2014/2012	2014/2008
Aricept	286.5	238.5	219.5	0.99	0.83	0.92	0.76
Radicut	8136	6695	5729.3	0.99	0.82	0.86	0.69
Rilutek	1701.5	1701.5	1536.8	1.00	1.00	0.90	0.90
Ceredist	1178.9	1178.9	1076.6	1.00	1.00	0.91	0.91

sified by the disorder they were developed to treat are shown in Figure 2. About half of all the neurological drugs were for the treatment of major diseases such as Parkinson's disease and epilepsy; however, as much as 10% were "other" drugs. Accordingly, this steady launch of new neurological drugs has successfully allowed urgent medical needs to be met, indicating that Japan is comparable to the US in the development of neurological drugs.

The profiles of all orphan drugs for neurological diseases ranked in top 500 in sales in the Japanese pharmaceutical market in 2014 are shown in Table 1. The top selling orphan drug in Japan was Ceredist. Notably, the drugs whose generic counterparts had already been launched in Japan (Ceredist and Rilutek) were still ranked in top 500 in sales. Fluctuations in the prices of Ceredist, Rilutek, Aricept and Radicut are shown in Table 2. The generic counterparts for all of these drugs have recently been launched. The prices of Rilutek and Ceredist did not change as much as those of Aricept and Radicut, even after the launches of their generic counterparts. In contrast, dramatic price erosion was seen for Aricept and Radicut after the entry of their generic counterparts to the market. Figure 3 shows changes in the clinical use of Rilutek, Ceredist, Aricept, and Radicut between 2009 and 2014 based on the number of prescriptions. Although the clinical use of Aricept and Radicut decreased after their generic counterparts became available, this was not the case for Rilutek and Ceredist, suggesting that these drugs are less susceptible to generic erosion than conventional drugs. Moreover, our results suggest that orphan drugs for neu-

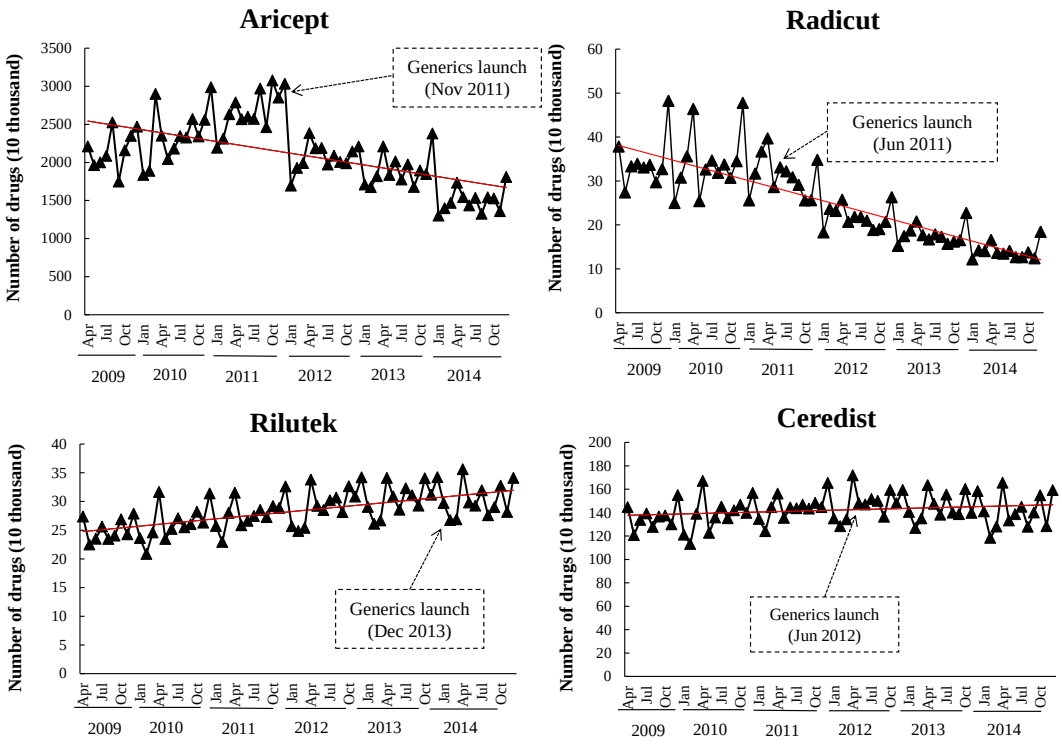

Figure 3: Changes in the clinical use of riluzole (Rilutek), taltirelin (Ceredist), donepezil hydrochloride (Aricept), and edaravone (Radicut) between 2009 and 2014

rological diseases can cultivate stable sales and largely remain free from regular price reductions.

4. Discussion

Basic research on orphan drugs has been encouraged by the establishment of a global network and a platform that supports pharmaceutical companies in the development of orphan drugs[27, 28]. In addition, more and more academic institutions are conducting research on orphan drugs[29], and as a result, numerous target molecules have been identified; this is expected to lead to the development of innovative new drugs for neurodegenerative diseases[30]. Based on quantitative analysis, new concepts for the effective clinical development of orphan drugs have also been developed[31]. Furthermore, research is increasingly being conducted in the field of clinical pharmacology, which is key as part of a complete clinical data package for new drug applications, mainly at the lower range of the prevalence-rate range[32]. Compared with orphan drugs in other therapeutic areas and non-orphan drugs, market approval of orphan drugs for neurological diseases required fewer clinical trials[33]. Accordingly, the development of orphan drugs globally has been markedly increasing. In this study, we found that the clinical development of neurological drugs led to the availability of numerous new drugs with stable sales in Japan, even though the cost of research and development in this therapeutic area is known to be high[34].

It is reported that dividing a major disease into a more specific variety of rare disease categories can stimulate drug development for the primary indication through the drug repositioning[35, 36]. In fact, one report describes this type of marketing strategy for orphan drugs[37], and another recommends that this strategy be applied to all orphan drugs in the future[38]. Our findings suggest that this type of marketing strategy works well, at least for neurological drugs in Japan if the drug repositioning is properly conducted. We hope that pharmaceutical companies in Japan will utilize these findings and develop innovative new orphan drugs across all therapeutic areas.

However, it should be noted that the following two issues have been raised: ethical considerations regarding the use of orphan drugs, and the effect of orphan drugs on health care costs. First, due to their low incidence, orphan drugs are more likely to be approved with less evidence compared with conventional drugs. Patients with orphan diseases may also receive less efficacious and riskier therapies[39]. In fact, a higher incidence of safety issues in relation to orphan drugs has already been reported[40]. To close this evidence gap, it is therefore necessary to utilize post-marketing studies [41–43].

Second, therapies for orphan diseases are often too expensive. Numerous discussions have been held to justify these high drug prices, most of these revolving around the fact that substantial investments have been made for small groups of patients[44]. One reported solution is the introduction of more

incentives for pharmaceutical companies so that drug development for rare diseases can be on par with that for major diseases[45].

Funding for clinical development has also been discussed. James *et al*[46]. reported that a more adequate funding system was needed to encourage drug development. All in all, orphan drug development is still faced with a number of challenges. However, we believe that adaptively optimized circumstances for both patients and society will be set in the near future.

In summary, numerous pharmaceuticals for refractory or rare neurological diseases have been launched in Japan over the past decade, and the development of such drugs has been noticeably increasing. However, the number of therapeutic agents available on the market in Japan remains low. In this study, we focused on Ceredist and Rilutek, which stop the progression of, but do not provide a cure for, neurological diseases. Therefore, innovative new orphan drugs that can actually cure neurological diseases are still needed in Japan. As long as the success rates for the development of new drugs remains low, pharmaceutical companies should employ a strategy of developing drugs for niche areas such as intractable and rare neurological diseases. This will allow pharmaceutical companies not only to survive in the increasingly competitive pharmaceutical market, but also to contribute to the advancement of public health.

5. Conclusions

The following findings were obtained from this research: 1) Marketing approval for drugs in niche areas such as rare neurological diseases has increased; 2) The number of intractable neurological diseases is large compared with other therapeutic areas, but the number of available therapies for neurological diseases remains limited; 3) Orphan drugs can be one of the top-selling classes of drugs in Japan. These drugs can cultivate stable long-term sales and are less susceptible to generic erosion than conventional drugs; and 4) Prices of orphan drugs for neurological diseases are likely to remain free from regular price reductions.

6. Author Note

This study was presented in part at Annual Meeting of The Japanese Pharmacological Society, March 10, 2016, Kanagawa, Japan.

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8. Conflict of Interest

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9. Article Information

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