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Review

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Non-Medical Hurdles for the Development of Causal Treatments in Neurodegenerative Diseases?

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Abstract

Neurodegenerative Diseases (NDDs) occur when nerve cells in the brain or peripheral nervous system lose function over time and ultimately die. The risk of being affected by a neurodegenerative disease increases drastically with age. With increasing life expectancy neurodegenerative diseases have been on the rise. The absence of a cure for NDD implies a high burden to the individual patient but also a tremendous cost to society.

This article advances some possible economic explanations for the absence of disease-modifying treatments for NDDs by exploring relevant non-medical hurdles in research and development. While the development of disease-modifying treatments for NDDs may present intrinsic hurdles existing economic research provides arguments why other explanations for the absence of causal therapies may play a role. Notably economic science can shed light on the incentives for developing causal treatments.

In this article we analyse the innovation inhibiting effect of an already existing drug portfolio. Moreover we demonstrate that different regulatory mechanisms in essence price controls and health insurance as well as patent protection might distort companies' incentives to innovate. This may tilt incentives towards research geared to smaller and lower incremental value innovations which could be an explanation for the lack of causal therapies in NDDs.

Keywords: Health economics • Pharmaceutical products • Innovation • R and D • Neurodegenerative diseases • Parkinson's disease • Alzheimer's disease

Introduction

Pharmaceutical products play a major role in improving health in modern societies yet for Neurodegenerative Diseases (NDDs), the pharmaceutical industry has been struggling to develop a causal or disease-modifying treatment [1,2]. NDDs are characterized by the progressive death of nerve cells [3]. NDDs usually occur at an older age but unlike in the physiological aging process the degradation of nerve cells progresses faster and to a greater extent. As a result massive impairments of mental and physical abilities occur [4]. Due to increasing life expectancy NDDs are becoming omnipresent leading to a tremendous social and economic burden to society. It is estimated that by 2037 Parkinson disease (PD) prevalence alone will be more than 1.6 million with a projected economic impact of over US$79 billion [5].

Among the neurodegenerative diseases are Alzheimer's Disease (AD), PD, and Amyotrophic Lateral Sclerosis (ALS). In addition rarer diseases such as Creutzfeldt-Jakob Disease (CJD) and Huntington's Disease (HD) fall into this group. The causes of pathological neuronal degeneration are not well understood. Although treatments may help relieve some of the physical or mental symptoms associated with neurodegenerative diseases there is currently no way to slow disease progression and no effective cure. The recent approval of the potential disease-modifying drug Aduhhelm (aducanumab) for AD could be a milestone yet also caused a stir in scientific community leading to the resignation of three FDA advisory panel members because of the lack of clear indications of the drug's efficacy [6, 7].

While the lack of effective disease-modifying treatments for NDDs might simply reflect the inherent medical difficulties of developing a cure there might also be economic explanations that render research in this area less attractive. The focus of this paper is to shed light on these possible explanations for the lack of causal treatments in NDDs. At the core of our hypotheses are the economic incentives of the pharmaceutical industry for conducting Research and Development (R and D).

Incentives for R and D follow a simple mechanism. Every R and D investment influences the return if R and D is successful an innovation occurs and a drug can be sold. A rational forward-looking investor will invest in R and D if and only if the expected returns surpass investment cost.

Expected returns in the pharmaceutical industry are most notably influenced by technological risk that is the probability of research leading to a marketable innovation. The perception of several failed attempts may discourage investment and even alternative approaches may no longer be implemented or implemented only with considerable hesitation. After several clinical trial failures for disease-modifying therapies this is exactly what happened in AD where research investments plummeted [8].

The expected returns of research investments are also influenced by other factors such as an existing product portfolio. Given that pharmaceutical companies typically produce a portfolio of drugs expected returns will consist of the payoff stream generated by the entire portfolio. Often these payoff-streams are not independent of each other in particular if the drugs are substitutes i.e., the same disease can be treated (albeit possibly in different phases of the disease). In this case pharmaceutical companies will also take into consideration the effect of the new drug on returns from other drugs in its portfolio. We show that the higher profits from existing drugs that

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run the risk of becoming obsolete if the new drug is successfully developed the lower a company's R and D incentives.

On the other hand price regulation or patent schemes also shape future returns in the pharmaceutical sector and hence incentives to invest in R and D. We demonstrate that price controls and health insurance as well as patent protection might distort companies' incentives to innovate towards smaller inventions with a low incremental value and lead pharmaceutical companies to be less ambitious in their research efforts.

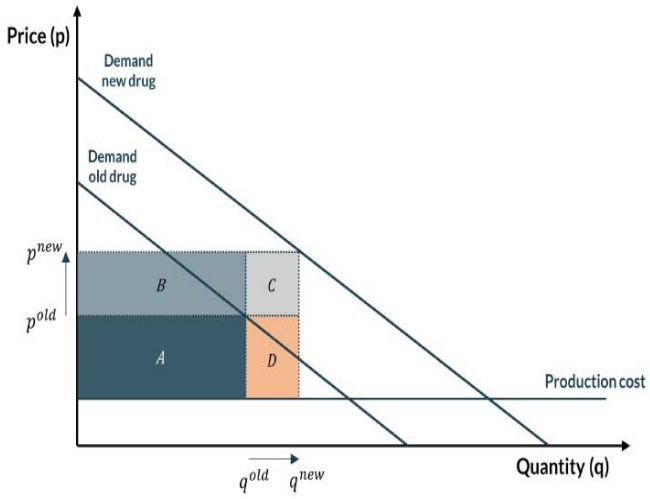
The remainder of the paper is structured as followed. In Section 2 we explain the effect of already existing drugs on the innovation process. In Section 3 we shift the focus and explain the effects of different regulatory mechanisms in essence price controls and health insurance as well as patent protection. Section 4 concludes.

How much innovation is expected in the presence of competing drugs?

As already indicated a company will evaluate the effect of a new drug on its existing product portfolio.The discussion on this section draws from Maier-Rigaud et al. (2020) and Lauer et al. (2021). One mechanism, that might be at play in this scenario, is the replacement effect [9]. The idea is rather simple a new drug can render an old one obsolete may it be due to its superiority in terms of efficacy tolerability or an easier route of administration. Alternatively also regulatory constraints such as reductions of reimbursement rates for the old drug can lead to its de-listing [10]. If so the new drug basically "cannibalises" the profits that a company made with the old drug prior to the invention of the new one. This effect is one of the possible concerns that competition authorities have in the context of pharmaceutical mergers. In that context competition authorities take a close look at product portfolios but also product pipelines and how they affect innovation post-merger in order to judge whether remedies are needed or the transaction may even have to be blocked.

Compared to the origins of the replacement effect focusing on process innovation we consider a replacement effect on product innovation [11]. For simplicity in describing the effect we assume a drastic product innovation that renders the existing drug obsolete. We make this assumption in order to explicitly model the maximum scope of the replacement effect knowing that a displacement is not necessary for such an effect to arise but also that in other settings other elements may mitigate the effects [12-16].

In the following framework we consider a company that sells an existing product protected by a patent generating a monopoly profit. If the company successfully develops a superior product the company's profit will increase. Figure 1 visualises the increase in profit due to the development of a new drug that replaces the old one abstracting from any up-front R and D cost or other factors such as health insurance or reimbursement rates. Starting off from the pre-innovation profit (area A) the increase in profit is made up of three components: a price effect due to an upwards shift in the price assessed at the original sales quantity (area B); a quantity effect due to demand expansion assessed at the original price margin (area D); and an interaction or combination effect due to both price increase and demand expansion (area C). In this figure the shift in demand can be rationalised as follows: The increased willingness to pay at any given quantity demanded can be attributed to the new product's superior qualities as for example measured by the gain in Quality-Adjusted Life Years (QALYs), and the increased quantity demanded at any price (including at a price of zero) reflects that the new product can serve patients that the old one could not.



Source: Modified from [17].
Note: The production cost is constant and assumed to be the same for new and old drug, i.e., no process innovation
Figure 1. Replacement effect

The larger the profits made with the old drug the lower the monopolist's incentive to innovate. To illustrate this point consider a simple numerical example taken from [1,2]. Assume that the new drug generates an expected profit of €120 m (areas A,B,C and D), while the old drug generates a profit €50 m (area A). Consequently the gains from innovation are €120 m-€50 m=€70 m (area C and D). If we now assume that that profit with the old drugs are smaller the gains from innovation increase. Thus the incentive to innovate increases if existing pre-innovation profits at risk of being cannibalised are low.

Can this mechanism be expected in the market of NDD treatments? Given that NDDs are typically treated symptomatically the development of causal or disease-modifying treatments might be an important improvement over existing treatments and might render the old drugs obsolete (at least for some patients). Impediments to the development of new drugs may be high when well-working existing treatments used by a substantial share of the affected population generate high profits. This effect might be present for instance with the drug Levodopa a symptomatic treatment for PD. Levodopa has first shown to cure symptoms of PD in 1961 and is still heavily used today accounting for a total revenue of around US$2.64 billion in 2020 [18-19]. Novartis a global healthcare company based in Switzerland reported net sales of US$600 million in 2010 for its PD treatment Stalevo (based on levodopa carbidopa and entacapone) [20].

In addition NDDs may often cause other conditions such as depression sleep disturbances or anxiety. For PD for instance in addition to the primary drugs for symptomatic treatment of the specific motor symptoms there is also a need for complementary drugs to treat the diverse non-motor symptoms such as constipation, urinary incontinence, sexual dysfunction, orthostatic hypotension, sleep disorders, psychiatric symptoms such as depression, psychosis and behavioural disorders, as well as cognitive disorders that affect a significant number of patients with advanced PD [21]. For instance direct medical costs for PD i.e., costs for PD treatment, as well as all follow up costs for other medication and health care interventions in ambulatory inpatient and nursing care are estimated to be as high as US$25.4 billion [5]. In the case of AD, prescription drug expenditures per year are roughly US$ 1,000 higher for people with AD compared to those without the disease

[22]. If one assumes that a superior causal drug reduces the chance of inheriting sequalaes this could well affect the incentives to innovate. This is because if a new superior drug is developed profits for treatments such as antidepressant or antianxiety drugs might decrease as well. Consequently it might be more beneficial to grant R and D subsidies to potential market entrants that do not face high replacement effects rather than incumbents.

Regulation

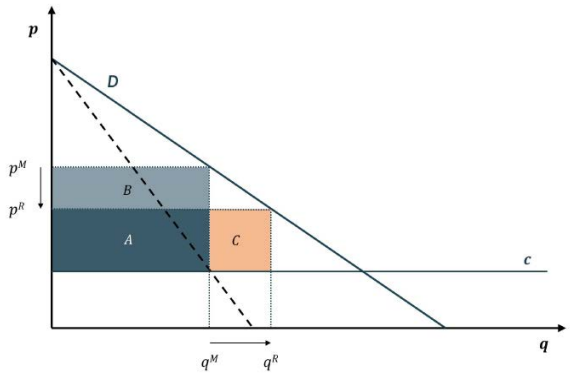
In this section we focus on two key regulations in public health, notably price controls, either in combination with or without insurance schemes and patent system regulations. Based on theoretical economic arguments we show how these regulations affect innovation in R and D and link the theoretical findings to existing evidence in the context of NDDs. In this section we draw from [1].

Price controls and health insurance

Economic theory provides indications for regulatory price constraints having adverse effects on innovation [23,24]. From an empirical point of view it is difficult to pinpoint and quantify the impact of regulatory restrictions on innovation as the following example shows. The US reported to have high levels of pharmaceutical R and D does also have a largely unregulated drug pricing market [25]. As such this seems to be consistent with the theoretical arguments that price regulation dampens innovation. This correlation however, does not rule out other explanations e.g. companies that focus on R and D may simply tend to operate from the US due to other corporate benefits or because they want to benefit from a large pool of talented scientists.

To determine the scope of price control effects it is important to consider the profit loss for the innovating company given a specific price regulation scheme. The following example illustrates how aggressive cost-containment policies can affect innovation decisions. A large innovation such as a first causal treatment for a specific NDD could potentially be marketed at a high price compared to a small innovation such as a further symptomatic treatment. If the large innovation faces more stringent price regulation than the small innovation for instance due to disproportional price reductions this can redirect R and D investments to the latter.

Figure 2 displays the effect of price regulation. Price controls impact profits in two ways. First it reduces the unregulated price p^M to p^R thus reducing profits (area B). Second the lower price increases the quantity demanded leading to an increase of profit (area C). The potential loss in profit due to the price effect is larger than the profit gain caused by the quantity effect resulting in a smaller regulated profit than the unconstrained monopoly profit.



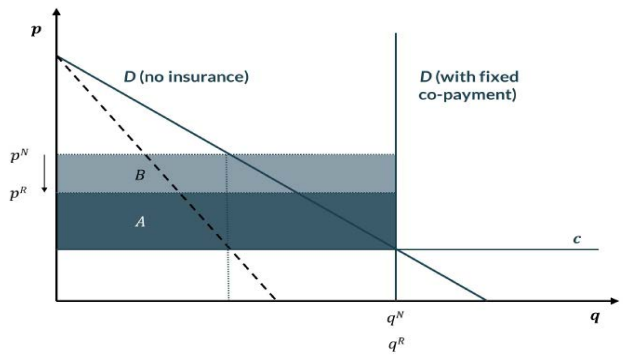
Source: Modified from [1].

Note: p^M is the unrestricted monopoly price. p^R is the regulated price

Figure 2. Effect of price regulation on profits

The introduction of health insurance schemes complicates the analysis of R and D incentives. Due to health insurance patients may not need to pay the full price for a specific drug. Instead they may either pay a fixed or proportional co-payment lower than the drug's price leading to a less elastic price demand. The price elasticity of demand measures the percentage change in the quantity demanded following a 1% increase in the price of the product in question [26]. In the case of insurances where the insurer pays the full price or in which patients contribute a fixed co-payment the demand from the patient's point of view becomes perfectly elastic i.e., an increase in a drug's price does not affect the patient's demand for that drug. If patients are insured with a proportional co-payment however, a drug price increase will reduce their demand. Obviously this effect of a decreasing demand is even stronger if a patient is not insured. It follows that ceteris paribus insurance increases a patient's demand for a given drug. In this case insurance causes an increase of company's incentive to innovate [27,28]. Notably the reverse can happen if insurers exert countervailing buyer power or even in the case of centralised public insurance monopsony power. As this would lead to pressure on drugs' prices in a similar vein as regulation [29,30]. Country-specific price controls can lead to a free-riding problem. On the one hand the investment costs need to be recouped on a global level but on the other hand each country could have a unilateral incentive to "free-ride" by covering only the marginal cost of production [31]. This in turn can cause underinvestment.

The preceding argument is illustrated in Figure 3 where a fixed co-payment equal to the level of the per-unit cost c is considered. This means that utilisation of an existing drug is efficient in the sense that all patients with a willingness to pay at least as high as the cost of production consume the drug. If drug prices are above the per unit-cost then the insurer pays the markup. This results in a situation in which at least from the consumer's perspective the company could set any price because with a fixed co-payment scheme patients are unaffected by any further price increase (as long as it does not feed back into their insurance rate). As such we denote the price that is negotiated between a company and the insurer by p^N. Figure 3 shows that the insurance enables the company to generate a higher profit for any given price greater than c. Again as shown in the previous example the regulated price is lower than the negotiated price thus replacing it effectively. The crucial difference is that with a fixed co-payment no quantity effect exists. Thus lowering prices has no effect on the drug demand and hence the company could not sell the drug to more people. In this framework any price regulation leads to a profit decrease (visualized by area B). In practice there can be quantity effects e.g. if too stringent regulation leads a company to delay or avoid entry in a specific market (country) or retreat from it or if certain drugs are exempted from the insurance coverage. Also note the assumption of fixed co-payments used above. With proportional co-payments changes in drug prices feedback directly into consumers' expenses and may therefore lead to quantity effects.



Source: Modified from [1].

Note: p^M is the unrestricted monopoly price. p^R is the regulated price

Figure 3: Effect of price regulation and insurance on profits

In both settings a price regulation leads to lower incentives to innovate.

However, whether a company focuses on small or large innovations depends on the exact price regulation mechanism. If as previously stated a disproportional price reduction is in place then this can in turn redirect R and D investments towards small innovations. Yet with clever price setting regulation an opposite effect could be induced. If one assumes that prices for large innovations are less strictly regulated than small innovations this should shift incentives towards large innovations accordingly. As discussed existing insurance schemes can either amplify or dampen the innovation incentives. Price regulations may moreover interact with the patent system another regulatory instrument that is discussed next.

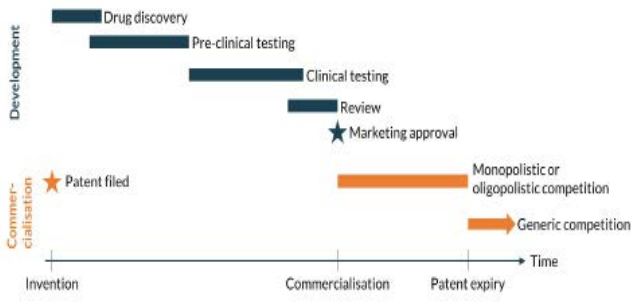
Drug development and patent system

As already mentioned the patent system also shapes future returns on investment. This section demonstrates that the interplay of length of clinical trials and the design of the patent system might lead to a distortion of incentives to innovate away from drugs with lengthy clinical trials towards drugs with shorter clinical trials and possibly smaller incremental value. The discussion of this section draws from Maier-Rigaud et al. (2020) and Budish et al. (2015) [32]. Empirical evidence suggests that research investments are distorted away from long-term projects in the case of cancer [32]. Further motivation is drawn from the observations that "certain types of medicine–for example drugs for long-term use and prevention of disease drugs to stop progressive or degenerative diseases and drugs for early stage cancer–are more likely to require longer research and development programs" and that "there are significant differences in the length of the average clinical testing period by therapeutic category; for instance central nervous system drugs, antipsychotics, antidepressants, anticonvulsants, and anti-Parkinson's agents take significantly longer in clinical testing than antibiotic and antiviral drugs. Drugs intended for acute use take less time to develop than drugs intended for chronic use and there may be a correlation between the pharmacologic class of a drug and the length of the clinical timeline" [33,34].

As shown in Figure 4, the lifecycle of a drug can be divided into two key stages: The development stage and the commercialisation stage. The development stage consists of a lengthy process involving drug discovery, laboratory development, animal studies, clinical trials, and regulatory registration. This lengthy process is necessary to ensure the efficacy and safety of the drug. It takes about 10-15 years to develop a new medicine from the time the active substance is discovered to when it is available for treating patients [35]. The average cost to research and develop each successful drug is estimated to be US$800 million to US$2.6 billion [36]. These stages often take many years of research and development and marketing approval is uncertain [37]. For instance several thousands of medicinal candidates are tested on average for one drug to be approved [38]. The drugs intended for long-term use consistently require longer clinical programs. These include among others treatments for AD, PD and other NDDs [34]. The challenges that arise in the discovery stage can be manifold. In the case of PD, for example one challenge is that "up to 15% of individuals taking part in clinical trials may not have Parkinson's. They are extremely unlikely to benefit from the new therapies being tested and their inclusion can affect both the trial results and ultimately the future of the potential treatment. Because Parkinson's is a progressive condition caused by the gradual loss of cells in the brain the best chance to intervene with treatments that can slow, stop or reverse the damage is during the earliest stages of the condition. However, during these early stages symptoms tend to be mild which makes selecting the right people to participate in trials very dificult" [39]. These dificulties are also prominently relected in the case of AD where between 2002 and 2014 99% of the tested drugs did not show any drug-placebo-difference and only one drug was approved by the US Food and Drug Administration [40].

In the commercialisation period pharmaceutical products typically undergo two stages of competition: Monopolistic or oligopolistic competition during the patent protection period and more intense oligopolistic competition by generic entry thereafter [30]. Although a patent does not shield the patentee from competing innovations competition usually drastically intensifies in the post patent period when generic entry is allowed. Generics offer chemically identical products i.e., products based on the same Active Pharmaceutical Ingredient (API) and the prices of generic drugs are typically substantially lower than prices of in-patent drugs. Empirical evidence indicates that drug prices decrease significantly after patent expiry with drug price ratios ranging from 6.6% to 66% 1 year–5 years after patent expiry [41].

The fundamental idea of the patent system is to increase incentives for new innovations by awarding the successful inventor with a period of exclusivity typically implying reduced competition and hence higher returns. All else equal the longer this period the higher the incentives for innovation [42]. Please note that the discussion abstracts from other elements that may shield the patentee from competition including: Regulatory exclusivity through the granting of an orphan drug status where during a certain period no new drugs can be approved for the same rare disease indication; regulatory exclusivity such as data exclusivity barring others from relying on the safety and efficacy data generated by the innovator; and natural barriers as in the case of large-molecule biologic products which may be more difficult to imitate [30]. Furthermore, the discussion does not consider potential patent litigation processes and its corresponding effects on patent duration or patent revenue [43].



Source: Modified from [1].
Figure 4: Life cycle of a new drug

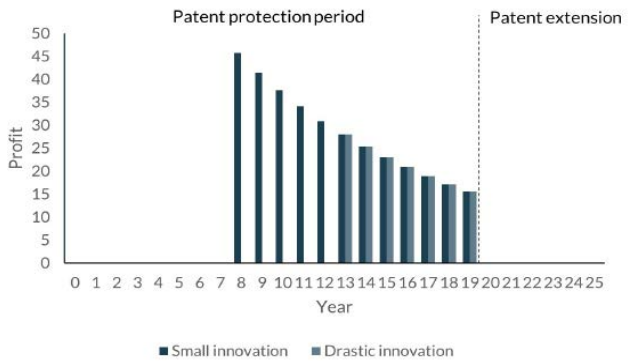
In the US, the Hatch-Waxman Act, more formally the Drug Price Competition and Patent Term Restoration Act of 1984, provides a baseline period of patent protection of 20 years [37]. It also grants innovators an extension of half of the time spent in clinical trials plus the full time spent in the review period. This extension can be up to 5 years but total market exclusivity from the point of marketing approval cannot be longer than 14 years. Time spent in pre-clinical trials cannot be recovered.

The moment of a patent's filing basically determines the effective patent period i.e., the years a drug is commercialised until patent expiry.Filing at the time of commercialisation gives a longer patent duration but is highly risky, which is why patents are usually filed much earlier in the development phase, typically before commencement of clinical trials [37,44]. Setting aside possibilities of extending the patent period the effective patent protection period is reduced by the number of years required to commercialise the drug.

Several additional factors affect the temporal profile of returns from the sale of the drug. First the interest rate, second, the possibility of managerial impatience, third, the risk that the innovation will become obsolete before the patent protection period expires and fourth, a growth rate, which measures the annual increase in profits. All these factors influence the discount factor that allows measuring today's value of tomorrow's return.

Finally for simplicity we assume the drug to be perfectly imitable (including the brand value), i.e., perfectly vulnerable to generic competition. Under these conditions the entry of generics reduces the company's profits to zero immediately after the end of the patent period.

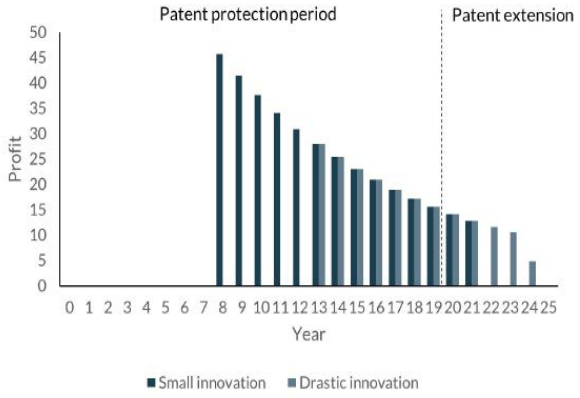
Figure 5 depicts two hypothetical scenarios for expected profit at the time of discovery (i.e., at the time of patent application): A small innovation with an 8 year commercialization delay; i.e., a period of 8 years between the patent application and the start of the marketing phase including 4 years of clinical testing; and a major innovation with a commercialization delay of 13 years of which 9 years are taken up by clinical trials.



Source: Modified from [1].
Figure 5: Profits without patent duration extension

In Figure 5 a patent is filed in year 0. If the innovation can be marketed quickly profits are positive from the 8th year onward. If the innovation is late to commercialize the company will not generate returns until the 13th year after discovery. From this point in time and until the end of the patent period both innovations are assumed to generate the same profit per period. Lastly when generics enter the market in year 20 profit is zero by assumption. Figure 5 highlights the importance of the effective patent protection period on overall profitability. It also demonstrates that it may be more worthwhile to invest in innovations with smaller incremental value.

One could argue that the extension of the patent period could solve the potential distortion towards smaller innovations as a longer patent extension can be granted the more time spent in clinical trials and in the review period. As our example shows this is not necessarily the case: Suppose now abstracting from any time spent during the review process that the innovator is granted an extension of half a year for every year spent in clinical testing. Clinical testing accounts for 4 years for the small innovation and 9 years for the large innovation. Hence patent extensions of 2 years and 4.5 years are granted respectively. Figure 6 expands on that example.



Source: Modified from [1].
Figure 6: Profits with patent duration extension

Such a short extension of the patent period has a relatively small impact on the overall profitability for both the small and the drastic innovation. The incentive to invest in a small innovation instead of a large one can be mitigated by a patent renewal but the effect might be small. There are two main reasons for this: First the patent extension may not fully compensate for the additional time required for clinical studies but only a fraction of it. Second the additional profits from a patent renewal will continue to accrue in the future and will therefore be discounted more heavily due to the interest rate and the risk of obsolescence. A few years lost due to a prolonged commercialization delay can have a similar impact on profits as a larger number of years of patent protection at a later stage. Therefore, differences in development time for different types of drugs and / or diseases can encourage a company to shift its R and D efforts to innovations with low incremental value.

In addition corporate short-termism can lead to excessive discounting leading decision-makers to focus on R and D projects that amortise quickly. For a brief introduction on short-termism see e.g. [45]. For more recent empirical contributions see e.g. [46,47].

Please keep in mind that these results do not prove that innovations with a short commercialization lag will always be preferred to innovations that go through a long clinical trial period but rather that this may be the case. Innovations of the latter type for example can generate higher profits because they are potentially more valuable countervailing and possibly overcompensating the effect described above. However, larger innovations could also require higher investments or may arise with a lower probability rendering them riskier. Feldman (2018) does, however, find that there is a trend towards innovations with smaller incremental value [48]. Specifically 78% of the drugs associated with new patents between 2005 and 2015 were not new drugs but existing ones. This might support our theory above but might also be a reflection of company's incentives to delay competitive entry for as long as possible. One strategy to extend patent protection is known as 'ever greening'. Companies can artificially extend the patent protection by filing for additional patents sometimes on methods of producing or manufacturing the drugs or on other aspects. More complex ever greening strategies involve developing new formulations dosage schedules or combinations that can be used to obtain new patents [48]. One way or the other the patent system might distort a company's incentive away from large innovation toward smaller ones.

Discussion

We presented a number of economic mechanisms that are recognised as important factors influencing the R and D decisions of pharmaceutical companies. The presented theoretical arguments show that investment incentives towards drastic product innovations might be distorted by a number of potential factors resulting in fewer or no investments in certain areas. This could in part explain the current lack of causal treatments for NDDs as research in this area may be underfunded. Empirical research is needed in order shed more light on whether any of the mechanisms described here are in fact part of the explanation for the lack of effective treatments for NDDs. Currently this cannot be ruled out and appears rather likely.

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Conflicts of Interest

Authors declare that there are no conflicts of interest in this work.

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