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## The New Neglected Diseases?

### Policy Interventions Are Needed to Encourage CNS Drug Development

*Soeren Mattke, Erin Audrey Taylor, Lauren E. Hunter, and Andrew Mulcahy*

In December of 2013, UK Prime Minister David Cameron, in his role as the current G8 president, is hosting a G8 summit on designing a “new international approach” to encourage research and cooperation on dementia and Alzheimer’s disease (Alzheimer’s Disease International, 2013a). It might seem paradoxical that policy initiatives are needed to promote drug development for a well-known condition that has significant health, social, and economic implications. Are not pharmaceutical companies arguing that they are running out of common conditions to treat and therefore focusing on specialty drugs? Why are existing market forces not sufficient to attract investment into drug development?

We argue that not only Alzheimer’s disease but also other common central nervous system (CNS) disorders, such as schizophrenia and depression, are becoming “neglected” diseases, since drug research and development (R&D) is not proportionate to the untreated disease burden. For example, several companies (Pfizer, Merck, and Sanofi-Aventis) reduced their investments, and others (GlaxoSmithKline, Novartis, and AstraZeneca) have exited this area

entirely (Abbott, 2011). In this paper, we evaluate the causes of this disconnect between unmet need and investment and discuss policy solutions to better align drug development with policy objectives.

#### Why is the lag in development such a concern?

Common CNS disorders have a devastating impact on individuals, families, and society as a whole. An estimated 35 million people worldwide have Alzheimer’s disease, which robs individuals of their memory and cognition and causes severe mood changes and agitation (Alzheimer’s Disease International, 2013b). Depression affects an estimated 350 million people, with severe depression causing a loss of ability to function at work and socially (World Health Organization, 2012). An estimated 24 million people worldwide suffer from schizophrenia, a debilitating mental disorder that often starts in young adulthood and puts patients—and society—at risk for violence and self-harm (World Health Organization, 2013).

With an aging population, the incidence of these disorders, particularly Alzheimer’s disease, is projected to increase signifi-

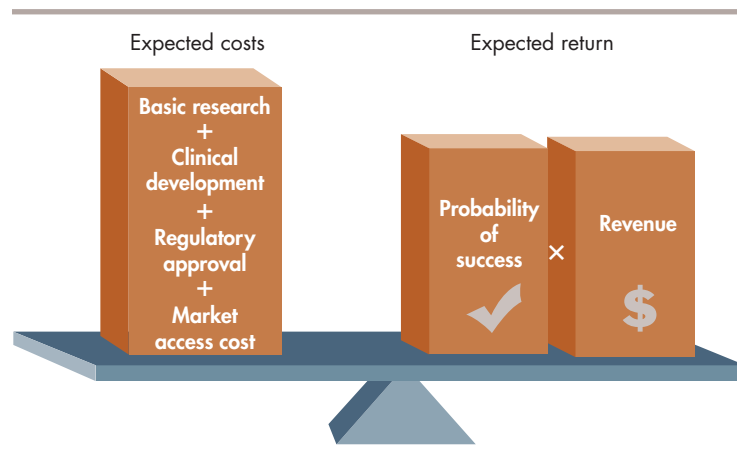
cantly over the next 30–50 years. Alzheimer’s disease is estimated to affect 115 million people by 2050—triple the number affected today (Alzheimer’s Disease International, 2013b).

The impact on society is also large: Severe mental disorders, of which depression and schizophrenia are the most common, have been estimated to cost society \$2.5 trillion worldwide on an annual basis, and this number is estimated to increase to \$6 trillion annually by 2030 (World Economic Forum & the Harvard School of Public Health, 2011). A RAND study estimated U.S. costs of dementia, of which Alzheimer’s disease is the most common cause, to be somewhere between \$157 billion and \$215 billion in 2010 alone (Hurd, Martorell, Delavande, Mullen, & Langa, 2013). Worldwide, societal cost of dementia has been put at \$604 billion per year (Alzheimer’s Disease International, 2010). If these costs represented a country, it would rank as the world’s 18th largest economy (Alzheimer’s Disease International, 2013b).

### Why is CNS drug development lagging?

Drug development has become a lengthy, high-risk enterprise: Only a handful of candidates that are screened enter clinical trials in humans, and of these, only about one in five are ultimately approved by the U.S. Food and Drug Administration (FDA) (DiMasi et al., 2010). Estimates of the cost involved in bringing a new drug to market range from hundreds of millions to low billions of dollars (Morgan et al., 2011). Many of these estimates include the cost of capital investments and of failures, which highlights the long timespan and risk intrinsic to drug development. Because of the uncertainty, cost, and length of drug development, pharmaceutical companies have become very deliberate in allocating investment capital to drug candidates that show a high likeli-

**Figure 1: Research and development investments balance a number of factors**



hood of returning that investment, as depicted in Figure 1. Innovators weigh the cost of development and probability of success against expected sales and only move forward the drug candidates that have the greatest profit potential. And for CNS drug development, this calculus is not favorable.

High development costs

The cost of bringing a drug to market is particularly high for CNS drugs. Figure 2 compares estimated new drug development costs, including the cost of capital, for several therapeutic areas. In these estimates, CNS drugs have development costs that are nearly \$100 million higher than the average cost of drug development (Miller, 2010). Longer development programs, more trials to meet FDA expectations, and challenges in recruiting and monitoring patients with common CNS conditions could explain those differences.

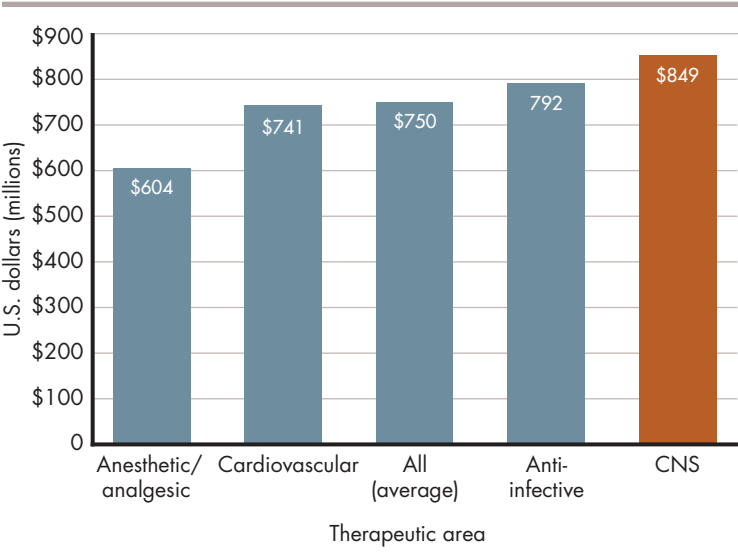
Low likelihood of success

In addition, a higher rate of failure during development for CNS drugs makes it difficult to justify the higher investment. In Figure 3, we plot the probability of success, defined as a product progressing from preclinical research through FDA approval against the average sales of FDA-approved molecules in 11 different therapeutic areas.<sup>1</sup> CNS drugs have one of the lowest probabilities of successful development. Only oncology and immunology products are similarly risky, but they have more than twice the average annual sales of CNS

<sup>1</sup>: The probability of success is measured at the compound level and encompasses a time frame from preclinical testing phase through to market approval. It is important to note that other estimates of success focus on different phases of drug development, which may make it difficult to compare across studies. Also, the average sales estimates shown here are at the molecular level and are for branded drugs only.

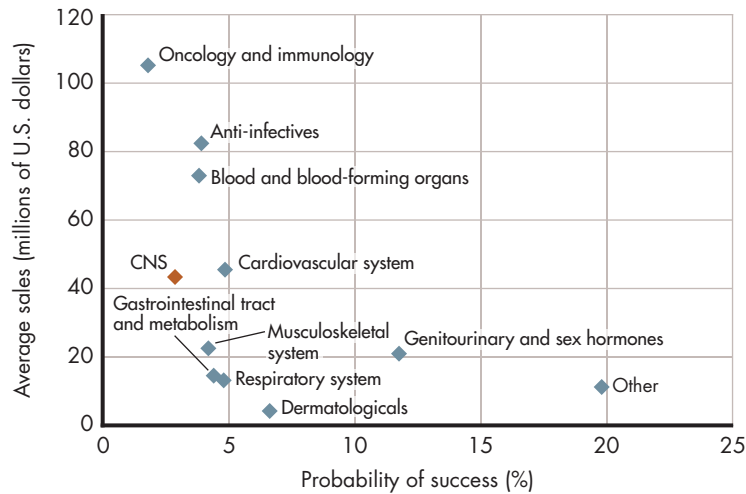
*Innovators weigh the cost of development and probability of success against expected sales and only move forward the drug candidates that have the greatest profit potential. And for CNS drug development, this calculus is not favorable.*

Figure 2: Clinical development costs, by therapeutic area



SOURCE: Miller, 2010.

**Figure 3: Average pharmaceutical sales compared with the probability of success, 1990–2007**



SOURCE: Pammolli, Magazzini, & Riccaboni, 2011.

products, compensating for the higher risk (Pammolli, Magazzini, & Riccaboni, 2011).

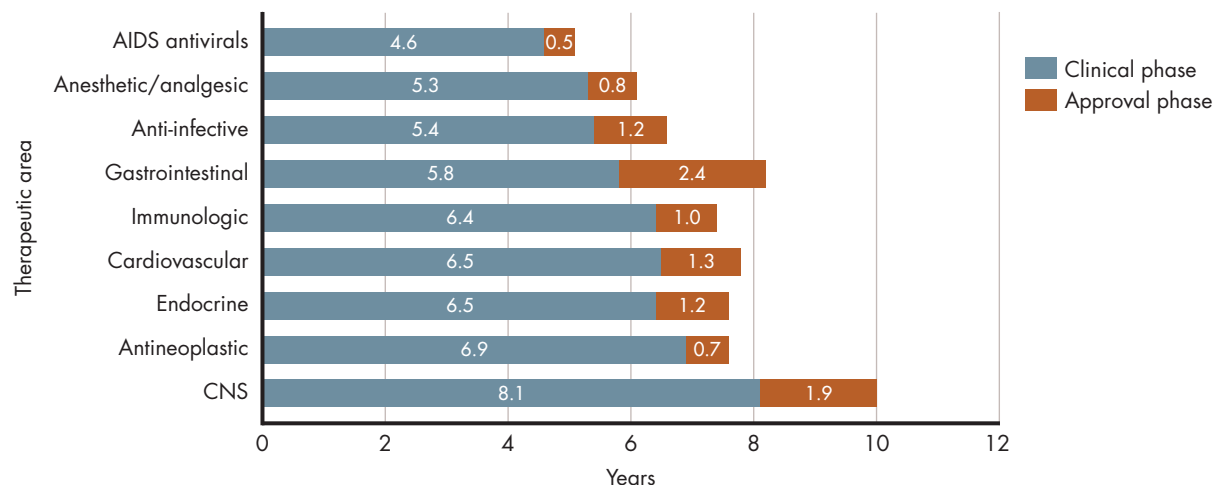
### Limited returns

In addition, the expected returns from an approved CNS drug are lower than in other therapeutic areas. First, the longer development duration, as shown in Figure 4, may shorten the effective on-patent life for CNS drugs (as compared to drugs used to treat other conditions) and thus reduce the timespan over which the initial investment can be recouped. While drug developers receive patent extensions to make up for time spent in clinical trials and regulatory review, the extensions are capped at a total of five years.

Second, the existence of imperfect but inexpensive treatment options for some conditions (e.g., depression) can limit both sales volume and profit margins. Payers tend to accept higher prices for so-called “first-in-class” drugs (i.e., those for a previously untreatable condition) than for “best-in-class” drugs that improve upon existing alternatives with respect to efficacy, side effects, and convenience.

This confluence of higher development risk, higher cost, and lower expected revenue explains why companies invest less in CNS drug development than would be desirable from a public policy perspective, given the high prevalence and substantial consequences of CNS disorders for patients, their families, and society. So the question arises: What policy interventions could be used to change

**Figure 4. Mean clinical and approval phase times for approved drugs, 2005–2009**



SOURCE: Kaitlin and DiMasi, 2011.

the trade-off for companies to attract investment in drugs targeting these neglected diseases?

## Policy levers to encourage CNS drug development

### Increase the probability of success

Drug-development efforts targeting diseases for which the biology is not well understood have a lower probability for success. Compared to cancer, for which drug development is commonly directed towards a defined mutation with a well-researched role in tumor growth, the causes of many common CNS disorders are not nearly as clear (National Institute on Aging, n.d.). It is established that amyloid deposits play a role in Alzheimer's disease and that neurotransmitter imbalances do so in schizophrenia and depression, but

we have not been able to pinpoint the exact nature and sequence of these diseases' biologies. This limited understanding makes it difficult to identify targeted therapies (and the biomarkers that indicate their effect), as recent late-stage failures for Alzheimer's drugs have shown (Doody et al., 2013; Armstrong, 2013).

Public policy efforts can help bridge this knowledge gap: Small policy changes can help to expand the subset of diseases eligible for dedicated programs and funding, thereby expanding the number of R&D projects being pursued for CNS disorders. Publicly funded research can be directed towards projects that improve the scientific basis for the development of pharmaceuticals targeting CNS diseases. By encouraging research into the biological mechanisms behind a disease, as well as the biomarkers that can be used to measure the effectiveness of treatment, funding agencies can help

to create the scientific foundation necessary for the development of effective pharmaceuticals and ensure that we effectively match regulatory outcome measures required from clinical trials to findings from basic science and clinical practice.

And there are efforts under way to translate basic research into treatment. For example, the Affordable Care Act of 2010 authorizes \$500 million per year towards the development of a *Cures Acceleration Network* that provides grants, partnerships, and flexible research awards in an effort to address challenges associated with translational research (National Center for Advancing Translational Sciences, n.d.a). The Therapeutics for Rare and Neglected Diseases (TRND) program at the National Institutes of Health, begun in 2009, might also serve as a model to expand research for diseases affecting a greater number of people. This program creates “collaborations [that] offer an opportunity to partner with TRND researchers and gain access to rare and neglected disease drug development capabilities, expertise, and clinical/regulatory resources in a collaborative environment with the goal of moving promising therapeutics into human clinical trials” (National Center

for Advancing Translational Sciences, n.d.b). Finally, the MATRICS Initiative (Measurement and Treatment Research to Improve Cognition in Schizophrenia) launched in 2003 by the National Institute of Mental Health (NIMH) sought to encourage the development of “cognitive-enhancing drugs for people with schizophrenia,” (Wooding et al., 2013). The first phase of the project involved the clarification of cognitive measures in order to define a pathway to FDA approval for such drugs.

In addition to investments in basic and translational research, drug development can also be accelerated via public funding for clinical trials. By further assisting in the development process for drugs that present high risk and offer uncertain reward, governments can help to increase the likelihood that these drugs enter the pipeline, as well as the likelihood that they are approved. One example is NEWMEDS, a European public-private partnership designed to improve preclinical-clinical translation for developing drugs to treat depression and schizophrenia (Abbott, 2011).

### Reduce development cost

Policies to reduce drug-development cost have long been used to steer investment towards unmet treatment needs. In the United States, for example, the Orphan Drug Act of 1983 provides various provisions that reduce development cost—such as tax breaks, waived user fees, and development grants—for drugs that would treat fewer than 200,000 patients and could not recover their development cost under market conditions (FDA, 2013). For example, drugs for cystic fibrosis were developed with support from the Orphan Drug Act and now extend the life expectancy and quality of life for individuals with this disorder (Brennan and Geddes, 2004). Similar policies exist in Europe and they have the intended effect. In the United

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*By encouraging research into the biological mechanisms behind a disease, as well as the biomarkers that can be used to measure the effectiveness of treatment, funding agencies can help to create the scientific foundation necessary for the development of effective pharmaceuticals.*



States alone, more than 400 orphan drug products have come to market since the law was enacted in 1983, compared to fewer than ten between the years 1973 and 1983.

The FDA is increasingly moving in that direction. Various expedited review programs, as recently reviewed by Sherman and colleagues (2013), can decrease clinical development cost and speed up market approval. These pathways allow, for example, the approval of a drug based on its achievement of surrogate endpoints under the condition that the manufacturers continue trials to prove the clinical benefits. The FDA may use the accelerated approval pathway to assist in the development of drugs to treat Alzheimer's disease, although that has not happened as of this writing. Kozauer and Katz (2013) suggest that the FDA might allow the accelerated approval pathway to be used for drugs that demonstrate an effect on cognition, but not necessarily on function, for patients with early-stage Alzheimer's disease. Further information from the FDA is needed to help pharmaceutical companies determine whether to explore this possibility, including the definition of *endpoints* and a clear outline of the data required to show efficacy under the accelerated approval process.

### **Make payoff higher and more predictable**

Today, public and private payers are increasingly factoring comparative effectiveness considerations into their market access and reimbursement decisions. That is, to command a premium over alternative treatments, pharmaceutical companies must demonstrate that their product represents a significant improvement relative to the other products already on the market. While discouraging investment in “me-too” products, such value-based pricing can have unintended consequences: If companies do not have visibility into which criteria will be used to determine the value of their products, they

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*Both payers and policymakers can help reduce . . . uncertainty by communicating upfront their criteria for determining market access and reimbursement, helping drug companies to prioritize candidates for development accordingly.*

may shy away from developing drugs for therapeutic areas with existing treatment options, even if those alternatives are not satisfactory.

Schizophrenia and depression drugs present an example of this dilemma. Established treatment options for these two conditions have been around for many years. Most of these drugs are now available as relatively inexpensive generics, but given the limited understanding of the biologic mechanisms underlying these diseases, the established drugs have limited effectiveness (Abbott, 2011) and, in some cases, substantial side effects. But lacking a clear understanding of how value will be defined (for example, in terms of incremental effectiveness and/or improved side-effect profiles), companies might be reluctant to pursue development projects in these areas.

Both payers and policymakers can help reduce this uncertainty by communicating upfront their criteria for determining market access and reimbursement, helping drug companies to prioritize candidates for development accordingly. They can also offer guidance to drug developers on what prices to expect for drugs that meet their prespecified requirements for safety and effectiveness, and they could even guarantee prices and quantities for a drug that meets those requirements at the beginning of the clinical development period.

Such advance market commitments have been used to encourage the development of drugs for the other neglected diseases, such as malaria. In the CNS space, involving state Medicaid programs in those discussions would be critical, as Medicaid is a dominant purchaser of those drugs and has significant power to determine whether to cover the drugs on their formularies.

In addition, longer exclusivity periods, such as those provided by the aforementioned Orphan Drug Act, can have a substantial positive effect on investment decisions by increasing expected revenue.

## **Conclusions and lessons for other therapeutic areas**

Our brief analysis suggests that current market forces are stacking the deck against development of drugs for common CNS disorders, as the expected returns on investment are lower and more uncertain than those for, say, targeted cancer drugs. We propose several policy changes that could steer investment into drugs for these “new neglected diseases” by reducing development cost and uncertainty and increasing expected revenue.

We would argue that a smart and differentiated use of such levers—levers that have proven successful in attracting development funds to rare diseases, such as cystic fibrosis—could be used to align investment with policy objectives on a larger scale. Implementing a sliding scale to ensure that incentives for drug development reflect the burden of the untreatable disease they target could accelerate development of CNS drugs given the prevalence of CNS conditions.

Recent advancements in basic research for Alzheimer’s disease (Bahrapour, 2013) and a new grant designed to explore Alzheim-

er’s disease treatments using other clinical pathways (Belluck, 2013) suggest that policy may be shifting in support of efforts to close treatment gaps in this area. However, for other CNS disorders such as depression and schizophrenia, further focus and incentives are necessary to spur development.

There also is a larger lesson to be learned: CNS is not the only therapeutic area for which product development lags. The emergence of multi-resistant pathogens, for example, has led to an urgent call to develop new antibiotics. Rather than complaining about the fact that companies are not basing investment decisions on societal priorities, we would argue that policymakers, payers, and regulators should work together to create incentives that draw investments into areas they would like to see prioritized. Our analysis points to several policy levers—detailed above—that are successfully being used to close development gaps in other therapeutic areas, and greater and more creative use of those could increase overall social welfare. In an ideal world, policymakers, regulators, and payers would enter into a meaningful dialogue with researchers, patient advocates, and pharmaceutical companies on how to focus drug development on policy goals, resulting in investment decisions less driven by short-term commercial considerations. This ideal world would contain an institution that coordinates drug-development policy among and between different government agencies, civil society, and private drug companies, resulting in a coherent and consistent framework across government and industry for the development of needed pharmaceuticals.

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## About This Perspective

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