EDITORIAL

Paving the Long and Winding Road for New Medicines in Neurology

Percorrendo o Longo e Sinuoso Caminho para Novos Medicamentos em Neurologia

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DOI: https://doi.org/10.46531/sinapse/ED/220061/2022

The burden of neurological disorders is one of the largest unmet medical needs globally,[1,2] and it is clear that as our societies become older and more affluent, and expectations on individual performance and autonomy continue to rise, this is a challenge that our generation needs to address.

Diseases of the nervous system (including psychiatric conditions such as depression, bipolar disorder, autism and schizophrenia) are among the top 5 leading causes of disability and death worldwide, and in the past 30 years, the number of deaths has increased by 39% and disability-adjusted life-years lost by 15%.[3] Since these conditions are typically chronic and incurable, and not uncommon, the economic impact on society of nervous system disorders is very large, and fast increasing. In 2014, nine of the most common neurological disorders contributed an estimated $789 billion dollars to the annual cost of healthcare in the US,[4] and the total European 2010 costs of brain disorders were $798 billion, of which direct health care cost 37%, direct non-medical cost 23%, and indirect cost 40%.[5] Furthermore, these costs do not capture the associated burden on caregivers and family, not just in related mental and physical health stress, but also loss of productivity and indirect care costs.

Simply put, the world needs more and better medicines to help people living with diseases of the brain and nervous system. This is not to say that other non-pharmacological measures will not be necessary as well – for example, lifestyle modifications, regular exercise, or better diet and sleep hygiene, are known to have very significant benefits both in preventing as well as coping with these disorders – but for the large majority of common neurological and psychiatric disorders we still do not have medicines that cure or significantly improve symptoms or prevent decline.

After a period of optimism in the 1990 - the "Decade of the Brain"[6] - when several new medicines were approved, and significant investment was made in the field of neuroscience, including raising awareness for this field of medical research, in the last two decades the pace of innovation has not accelerated as fast as hoped. New, large-scale, government backed initiatives have been announced such as the Human Brain Project[7] or the BRAIN Initiative,[8] but while these are important efforts to advance the field of basic neuroscience, the translation of such findings into clinically relevant insights or medical advances takes a lot more time than politicians (and scientists) will usually admit.

Why is it so hard? The basic problem in drug development remains one of translatability, bridging the gap between basic science breakthroughs and clinical impact. This is not a new problem, but it is one that has proved very resistant to solutions, more so in neuroscience than in other fields. Almost 20 years ago, Sung and colleagues wrote about this topic, and their framing remains true: "[There is a] disconnection between the promise of basic science and the delivery of better health".[9] Analysis of this translational gap, looking both at percentages of success, as well as time gap

Informações/Informations:
Editorial, publicado em Sinapse, Volume 22, Número 3, julho-setembro 2022. Versão eletrónica em www.sinapse.pt; Editorial, published in Sinapse, Volume 22, Number 3, July-September 2022. Electronic version in www.sinapse.pt

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Recebido / Received: *2022-09-27*
Aceite / Accepted: *2022-10-09*
Publicado / Published: *2022-10-20*

to clinical translation (both positive and negative) does not show a significant or systemic change happening in recent years.[10] And when we look at the factors that predict translatability in drug development, it is easy to understand why neuroscience remains one of the hardest areas to succeed in: animal models do not have good construct or predictive validity; there is sparse and inconsistent real-world, natural history and genetic data; and most of all, poor surrogate biomarkers and endpoints, and lack of precision medicine approaches doom most clinical trials to failure.[11]

This is, unfortunately, still the reality for the most common neurological and psychiatric conditions such as stroke, Alzheimer and Parkinson disease, depression and schizophrenia. For a long time, the exception in neuroscience was, arguably, the development of medicines for relapsing forms of multiple sclerosis, where the predictive power of brain magnetic resonance imaging (MRI) as a surrogate in early trials (especially T2, and T1 Gd+ lesions) resulted in over 14 new molecular entities developed over the past 20 years – despite the poor predictive validity of the animal models commonly used in research.[12] But I think that even clearer lessons can be gleaned from another area where several significant advancements have happened in recent years. For rare diseases such as lysosomal storage disorders, rare inborn errors of metabolism, and evidently for spinal muscular atrophy, in the space of only a few years several highly effective drugs have been developed, approved and are globally available. This success speaks to the power of combining a deep understanding of disease pathophysiology (as several rare disorders are genetically driven), together with predictive animal models, the use of emerging new technologies and platforms that allow manipulation of biology at its fundamental level (e.g. antisense oligonucleotides, gene therapy and gene editing, splicing modulation), and clinical trials anchored on predictive surrogates and biomarkers, and adaptive regulatory pathways.[13] And when one looks at the rate of new discoveries in basic neuroscience, including genetics and genomics, new opportunities brought forth by the application of AI/ML algorithms to very large datasets, and the sheer volume of investment in biotech and research, there is a growing belief that drug development in neuroscience might be reaching an inflection point.[14]

What will it take to cross this inflection point? Among others, one key problem is the difficulty in accurately measuring behavior (motor skills, cognitive ability, mood, social interaction, etc.) especially in the "natural daily ecosystem" where patients live. As neurologists, we are trained in the art of accurately diagnosing and monitoring patients' disease course through an almost ritualized and time-proofed set of observations and tests, and rightly judge the exact performance of a neurological examination as one of the centerpieces that defines our profession.[15,16] Ancillary tests – imaging, electrophysiology, CSF profiling – are deemed important but not substitutive. However, these tests were not developed for use in clinical trials, and mostly do not have the required statistical performance characteristics; additionally, they are evaluated only sporadically during studies which further reduces our ability to detect the true effects of new drugs. Among the solutions we are starting to implement are digital endpoint platforms that patients and physicians can use to supplement clinical practice,[17] and also as endpoints in clinical trials, as was done in a recent Parkinson's Ph2 trial.[18]

Finally, it will take many more physician-scientists engaged in translational and pharmaceutical research. Having taken that step almost 15 years ago I acknowledge the difficulties in transitioning careers, but also the immense opportunity for impact that exists in pharmaceutical medicine.[19] Requirements for translational scientists include domain expertise and rigorous research skills, but also the ability to be systems thinkers, boundary crossers and team players.[20] Physicians are naturally trained to have most of these qualities, and most importantly they provide a unique perspective into what is clinically important and meaningful to patients – so we need to increase our participation in, and leadership of the long process that transforms science into medicines that help patients preserve what makes them who they are. ■

Responsabilidades Éticas

Conflitos de Interesse: Paulo Fontoura é atualmente funcionário e acionista da F. Hoffmann-La Roche.

Suporte Financeiro: O presente trabalho não foi suportado por nenhum subsidio o bolsa ou bolsa.

Proveniência e Revisão por Pares: Comissionado; sem revisão externa por pares.

Ethical Disclosures

Conflicts of Interest: Paulo Fontoura is currently an employee and shareholder of F. Hoffmann-La Roche.

Financial Support: This work has not received any contribution grant or scholarship.

Provenance and Peer Review: Commissioned; without external peer review.

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