COMMENTARY

Trickle-Down Therapeutics: Entitlement and Deprivation in the Treatment of Alzheimer's Disease

Donald F. Weaver

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Global diseases like Alzheimer's disease (AD) deserve globally available solutions – solutions without borders, be they geographical, political, ethnic, ageist, or socioeconomic. Sadly such will probably not be the case for AD. Although drug discovery has a long and successful history via a "trickle-down approach," recent realizations emerging from the worldwide management of the COVID-19 pandemic have again focussed a spotlight on our need to reevaluate the viability of the trickle-down paradigm as applied to devastating global health crises, with AD emerging as a disease of present and future concern.

The trickle-down effect is based upon the supposition that preferentially providing opportunities, resources or capital to a designated and usually privileged segment of a population (often categorized as "haves" or "influencers") will yield, via a trickle-down process, disproportionately greater benefits for their "have-not" counterparts than could be achieved by providing the same resources or opportunities directly to that same "have not" population; that is, when the "have" group gets richer and better-resourced, the "have-not" group experiences outsized positive effects being transformed from "have-nots" to "had-nots."[1] Within our polarized geopolitical and societal constructs, trickle-down effects are pervasive across many human activities. Pharmaceutical discovery is one such complex and diverse human activity; pharmaceuticals have traditionally been developed employing a "trickle-down therapeutics" model by which drug research occurs almost exclusively in select wealthy countries with a hope that these agents will eventually gain widespread international distribution.[2] This skewed approach to resource allocation is controversial with passionate supporters and vehement opponents; not surprisingly, it is hotly debated, most notably within the context of economics issues.

Trickle-down economics, also known as trickle-down theory, is the supply-side economics proposition which purports that improved monetary benefits for the wealthy trickle down to everyone else because supposedly the real drivers of economic growth are those with the track-record and know-how to effectively facilitate enhanced productivity output. This concept – though interesting and enthusiastically praised by the politically influential wealthy people to whom the benefits flow – has been an abject failure, rejected soundly by economists and the International Monetary Fund.[3,4] Repeatedly, it has been demonstrated that when the rich get richer, financial benefits do not trickle down, but rather the have/have-not chasm merely deepens and widens.

However, trickle-down economics is just one subtype within the conceptually broader spectrum of trickle-down effects, a notion pioneered by the 19th century German scholar von Jhering who analyzed such effects in terms of cultural diffusion, studying as a specific example the phenomenon whereby consumer fashions filtered down from upper to lower classes.[5] New consumer products are initially affordable only by the wealthy, but as the fashion product matures its price-point falls as a successful trickle-down fashion effect makes the product inexpensive and globally accessible to the general public in a timely manner. Can the rapid, affordable distribution of fashions be replicated through a pharmaceutical distribution chain in which cheap knockoffs are not acceptable?

Though the term trickle-down therapeutics has yet to be formally applied to the drug discovery process, therapeutics are clearly devised within a trickle-down effect context, being often designed for an affluent "have" population with the expectation that these therapies will ultimately trickle down to the "have-not" population. Given the expertise requirements and significant costs associated with drug development it is understandable that pharmaceutical creation has historically been performed in countries with developed economies and an established scientific infrastructure. In concert with this geographical imposition, greater attention is focussed on diseases relevant to those countries, rather than on major diseases which may be more common in developing regions. Moreover, even when drugs addressing globally prevalent disorders are developed, their international market penetration is often disappointing, regardless of need.[6]

The public health failings of trickle-down therapeutics are long-standing.[7] Small molecule drugs have long been the mainstay of pharmacology, and many can be produced for pennies per kilogram making this therapeutic modality an obvious choice when striving to achieve globally available therapeutics to serve everyone on our "pale blue dot in the cosmos."[8]

From the Krembil Research Institute, University Health Network, University of Toronto, Toronto, Ontario, Canada (DFW)

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Correspondence to: Donald F. Weaver, Krembil Research Institute, Krembil Discovery Tower, 60 Leonard Avenue, Toronto, ON M5T 0S8, Canada. Email: donald.weaver@uhnresearch.ca

Nevertheless, even such cheap and effective drugs are not readily accessible to many patients. Access to essential medicines is problematic for more than one-third of all persons worldwide.

When considering the anticipated future dilemma of attaining universally accessible therapeutics for AD, instructive insights are provided by another globally prevalent chronic neurological disease: epilepsy. Epilepsy has world-wide prevalence with 70%−80% of cases being in developing countries given that the risk factors for epilepsy are more common in these regions. Regrettably, despite the introduction of many new effective agents (e.g., clobazam, lamotrigine, levetiracetam, perampanel, topiramate) over the past 30 years in North America and Europe, the standard of treatment in developing countries remains phenobarbital – a less than optimal 1912 drug.[9] When it comes to treating epilepsy, the lessons learned, the newly identified druggable targets and the conceptual and practical advances of the past 50 years have simply not trickled down to benefit those in the developing world – despite decades of opportunity and need; and this is for epilepsy, a disorder of youth in a global community in which pediatric prevalence of disease attracts additional attention from international health organizations and public relations-focussed media outlets.

Arguably, the inadequacies of this trickle-down paradigm are set to become worse. The new frontiers in therapeutics development are dominated by biologics, stem cells, and personalized medicine. Though biologics have shown impressive efficacies targeting cancer and inflammatory diseases, they are large, complex molecules, produced using recombinant DNA technologies, and thus difficult to manufacture and distribute in lower-income countries, even as biosimilars.[10] At the next levels of complexity, regenerative medicine is employing stem cells to regenerate/repair diseased tissues in specific people, whereas precision medicine is tailoring specific products for specific patients based on their predicted responses and risk of disease.[11] Someday we shall be able to target individual drugs to individual people in rich countries, but will be unable to deliver basic medicines for entire populations in poor countries – a disturbing dichotomy arising from societal inequalities that nurture social unrest.

The public health shortcomings of trickle-down therapeutics have been starkly illuminated by humankind's most recent major disease: COVID-19.[12] Though the COVID-19 pandemic has produced many pros (multiple effective vaccines) and cons (hydroxychloroquine hoarding, vaccine nationalism, restricted biologics availabilities, oxygen shortages), the have/have-not inequities which characterize this pandemic have witnessed limited dissemination of trickle-down benefits into poorer countries; and this is for COVID-19, a communicable disease in a mobile world in which facile international travel facilitates disease transmission. Recently, a trickle of vaccines has slowly begun to make its way into some developing countries. However, such limited trickle-down generosity will probably not be forthcoming for another on-going, but non-communicable pandemic of the aged: AD and other dementias.

Dementia has a global prevalence of 50 million cases, and every 3 s there is a new addition – 60%−70% of whom live in low or middle-income countries where dementia risk factors are more common; socioeconomic factors, such as education and literacy, are directly linked to the rates of AD in the developing world.[13] Accordingly, AD is regarded as "the tidal wave on the horizon" particularly in the developing world which is experiencing unprecedentedly rapid demographic aging and in which health services are often already overwhelmed or non-existent.[14] Dementia presents a unique set of challenges for developing countries, challenges which cannot be ignored if we are to avoid the global unrest born of social inequalities. Unfortunately, the high cost of dementia drug development dictates that a scant trickle of these future agents will ever traverse borders to the poor, despite their escalating needs.

Drug discovery requires innovation, but innovation is costly and risky. Trickle-down therapeutics thus manifests as a challenging mixture of triumph and tragedy, lying bracketed between the failures of trickle-down economics and the successes of trickle-down fashion. Yet regrettably, when it comes to delivering safe, cost-effective therapeutics in a timely manner on the world-wide stage, trickle-down therapeutics lies clearly closer to the failure end of this spectrum. Within developed societies, trickle-down therapeutics has delivered many notable successes, and the creativity required to surmount the financial and intellectual risks of creating these successes must be rewarded to motivate the ongoing discovery of new, potentially life-saving medicines. As a model, trickle-down therapeutics generally thrives in modern, industrialized countries, but fails in poorer, underdeveloped nations; that is, if you are well-to-do the *status quo* works well, very well – yet sick people deserve care, regardless of nationality, age, ethnicity, or socioeconomic status, be they entitled or deprived.[15] Governments and society (including media/social media influencers) should collectively do more to rethink the current *status quo*: AD/dementia needs to be accepted and acknowledged as a global health crisis; policy makers need to prioritize dementia research, prevention and treatment, and to anticipate global future needs; meaningful dementia research in developing countries must be supported; new mechanisms for therapeutics development and distribution need to be pioneered; and lessons need to be learned from epilepsy, COVID-19 and other international public health issues. Global diseases deserve global solutions, and as currently implemented, the trickle-down therapeutics model fails to deliver global solutions. The burden of this failure in terms of human suffering and social costs has been and will continue to be enormous.

Competing Interest Statement

The author declares no conflict of interest relevant to this submission.

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