Reversal of Cognitive Decline: A Systems Approach

Topic: Using systems analysis to improve health research.
General Purpose: Informative – compare/contrast
Specific Purpose: To highlight the differences between monotherepuetic medical research and systems approach with a compare/contrast and case study
Thesis: A systems approach to medical research provides an exciting and novel method to develop alternative therapies in poorly understood diseases.

- Introduction
  - Attention Getter
    - Anecdote – Fuzzy slippers memory
  - Relevance Statement: Article in the journal Aging
    - Projection to 2050
    - RR to audience of getting AD: greater chance of breast cancer
  - Thesis Statement
    - A systems approach to medical research provides an exciting and novel method to develop alternative therapies in poorly understood diseases.
  - Preview of Main Points
    - Overview of Therapy Development
    - Systems: What we don't know
    - Case Study: Reversal of Cognitive Decline
- Body
  - **Overview of Monotherapy development**
    - <u>Primary Research: In vitro to animal sudies</u>
      - “New drug research starts by studying how the body functions, both normally and abnormally, at its most basic levels.” - FDA
      - “To this point, the search for a new drug has been confined to a laboratory test tube. Next, scientists have to test those compounds that have shown at least some desired effects in living animals.” - FDA
    - <u>Clinical Trials: Human efficacy and safety</u>
      - “Clinical trials, also known as clinical studies, test potential treatments in human volunteers to see whether they should be approved for wider use in the general population.” - FDA
      - “Although efforts are made to control risks to clinical trial participants, some risk may be unavoidable because of the uncertainty inherent in clinical research involving new medical products.” - FDA
    - <u>Costs and Results</u>
      - “These[AD] trial designs would be very challenging currently, as they might require a trial length of more than two decades” - Evolution
      - “The organization Pharmaceutical Research and Manufacturers of America estimates that only 5 in 5,000 compounds that enter preclinical testing make it to human testing, and only 1 of those 5 may be safe and effective enough to reach pharmacy shelves.” - FDA
  - **Transition: A problem arises: what do we do when we don't know the cause?**
  - **The Systems Approach**

- Poorly understood pathology
  - It is likely that our simplistic understanding of the AD pathophysiologic process based on current biomarker data will continue to evolve.
  - Second, it is possible that targeting a single pathway will be sufficient, but that earlier intervention will be required. Third, it is possible that all of these seemingly disparate pathways will converge on a single critical pathway, so that either a single targeted therapy or a multi-component, multi-targeted approach may be effective. - Reversal
- Multiple contributions
  - "Direct validation at the biochemical level came with the report by Ames et al in 2002, 26 mostly from experiments with cultured cells, that at least 50 human genetic diseases involving defective enzymes could be remedied by increasing available concentrations of a nutrient component of the coenzyme; the authors acknowledged Pauling's contribution." - Alternative
  - However, one of the drawbacks of these preclinical studies is that many have implicated single pathways, and shown large effects of targeting one pathway, whereas in human studies, such approaches have not been borne out. - Reversal
- Faillure of traditional monotherapeutics
  - "Furthermore, in the past decade alone, hundreds of clinical trials have been conducted for AD, at an aggregate cost of billions of dollars, without success." - Reversal
  - The five pharmaceutical drugs approved in the United States as primary AD therapies can slow the progression of some symptoms, but generally only for 6-12 months; half of all patients may show no improvement. - Alternative

- **Transition: How might we apply this process in practice?**
- **Review of this study**
  - Model of CD/AD
    - "However, the past few decades of genetic and biochemical research have revealed an extensive network of molecular interactions involved in AD pathogenesis, suggesting that a network-based therapeutics approach, rather than a single target-based approach, may be feasible and potentially more effective for the treatment of cognitive decline due to Alzheimer's disease." - Reversal
    - "Based on a combination of in vitro and in vivo studies, we have advanced a model in which AD results from an imbalance in endogenous plasticity signaling (Fig. (Fig.1),1), 5-9, and in which the β-amyloid precursor protein (APP) is a mediator of such plasticity-related signaling." - Reversal
  - Therapeutic Program
    - "The results also suggest that, at least early in the course, cognitive decline may be driven in large part by metabolic processes." - Reversal
    - "For each network component, the goal is to address it in as physiological a way, and as far upstream, as possible." - Reversal
  - Results
    - "Nine of the 10 displayed subjective or objective improvement in cognition beginning within 3-6 months, with the one failure being a patient with very late stage AD." -Reversal
    - "Thus the model suggests that AD is analogous to other chronic illnesses such as cancer, osteoporosis, and atherosclerosis." -Reversal

- Conclusion
  - Review of Main Points
    - Traditional monotherepeutics, from test tubes to humans, require billions of dollars, thousands of trials, and more than a decade to complete.
    - A systems approach to poorly understood diseases offers a cheap, safe, and fast alternative method for developing potential therapies.
  - Restate Thesis
  - Closure
    - Hopefully, with the potential applications of the systems approach, I might still remember all of your names when I am 90.

Bibliography

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- Sperling, Reisa, Elizabeth Mormino, and Keith Johnson. “The Evolution of Preclinical Alzheimer’s Disease: Implications for Prevention Trials.” *Neuron* 84, no. 3 (November 2014): 608–22. doi:10.1016/j.neuron.2014.10.038.