FDA drug approvals and combination therapy clinical trials

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Introduction

The most effective strategies to curb the rise of cardiometabolic diseases in the late 20th century focused on single risk factors. Population-level blood pressure and cholesterol, for instance, decreased in large part from pharmaceuticals [1,2]. The returns on these innovations now appear to be diminishing: obesity rates continue to rise [3], and gains in healthy life expectancy trail that of total life expectancy [4]. If these patterns reflect a broader depiction of the modern human condition, then we should question if such complex challenges can be addressed through such focused countermeasures. The primary question of interest here is how many approved therapies consist of multiple active chemicals or biologics.

Protocol

Drugs@FDA is downloaded from https://www.fda.gov/Drugs/InformationOnDrugs/ucm079750.htm, and a filter is created on drugs which are original Submissions, Prescription or Over the Counter Status, and an ANDA, NDA or BLA Application type.

Clinical trial metadata is downloaded from https://clinicaltrials.gov/AllPublicXML.zip, and a filter is created where trials are Not Yet Recruiting, Recruiting, Enrolling, Active, or Not Recruiting, and where Age Group is greater than 18, and an Interventional Study Type. A keyword search for 'combination' is performed in the study description.

Results and Conclusions

An overwhelming majority of FDA-approved drugs consist of one active compound, and clinical trials continue to rely on single drug interventions (Figure 1). Two primary forces likely drive this effect. The first is rooted in the overtly reductionist framework in biomedical research. Therapeutic-oriented research is primarily concerned with a one-at-a-time functional assessment, such as the role of a single protein in a signaling pathway, or single nucleotide polymorphism genotype-phenotype relationships. The second force is both the complexity and challenge in both designing and gaining approval for combination therapies. Combination therapy trials require more human subjects and cost, and must demonstrate greater efficacy over single therapies to win approval. Despite these challenges, there does appear to be a trend towards greater therapeutic complexity in recent years. This effect may highlight encouraging shifts in systems-level thinking in translational research and an innovative drive towards more effective therapies against hard-to-treat chronic conditions.

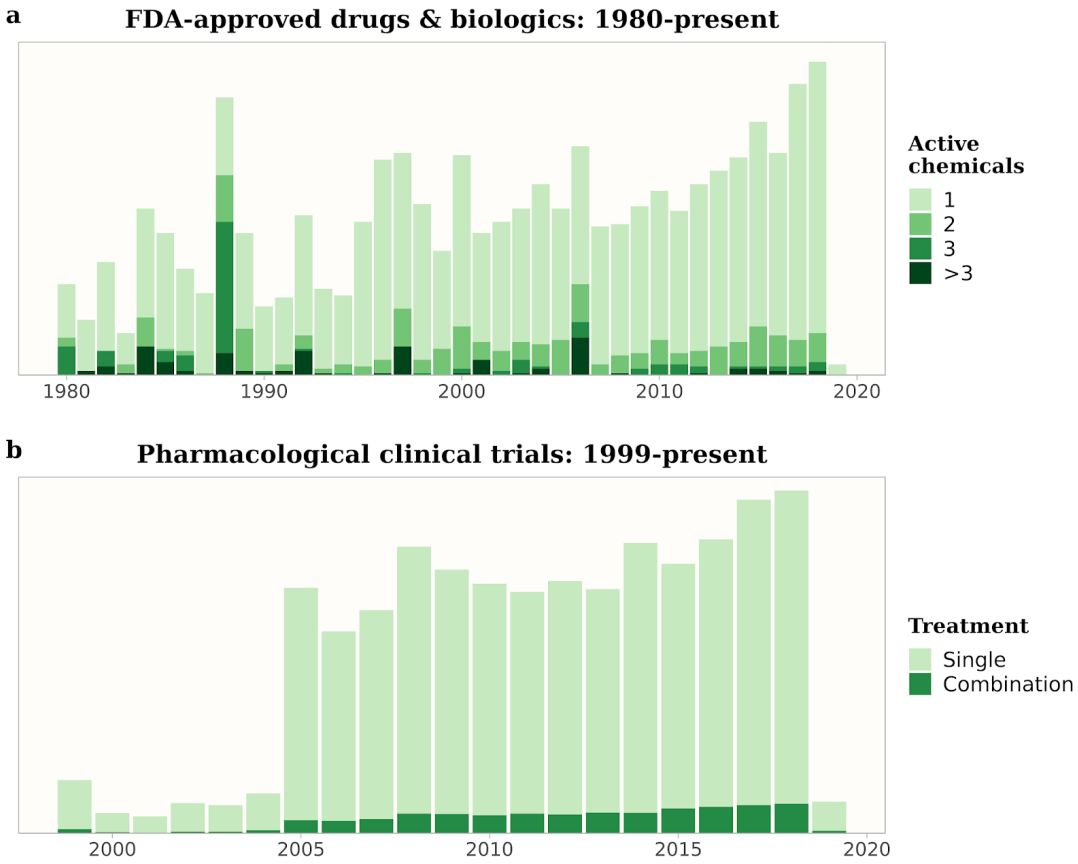

Figure 1. (a) Number of active ingredients in FDA-approved drugs and biologics, from 1980 to present. Data source: https://www.fda.gov/Drugs/InformationOnDrugs/ucm079750.htm. (b) Clinical trials which employ an interventional drug from 1999 to present (including active clinical trials, as of February 2019). Combination therapies were detected through a custom text-parser. Data source: https://clinicaltrials.gov/AllPublicXML.zip.

References

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