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DRUG METABOLISM & DISPOSITION

Special Section on Natural Products: Experimental Approaches to Elucidate Disposition Mechanisms and Predict Pharmacokinetic Drug Interactions — Commentary

National Center for Complementary and Integrative Health Perspectives on Clinical Research Involving Natural Products

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ABSTRACT

The sales of dietary supplements continue to increase year after year. Despite their use by a large percentage of Americans, there is little evidence for the vast majority of products regarding their safety or efficacy. National Center for Complementary and Integrative Health supports a broad range of research on dietary supplements, including clinical trials. Our experience with these trials has shaped our current policies and priorities for clinical research. This perspective outlines those policies and priorities that are shaping our investments going forward.

SIGNIFICANCE STATEMENT

The sales of dietary supplements continue to increase year after year. Despite their use by a large percentage of Americans, there is little evidence for the vast majority of products regarding their safety or efficacy. National Center for Complementary and Integrative Health supports a broad range of research on dietary supplements, including clinical trials. Our experience with these trials has shaped our current policies and priorities for clinical research. This perspective outlines those policies and priorities that are shaping our investments going forward.

Introduction

The sales of dietary supplements continue to increase year after year (New Hope Network, 2019), indicating the US public continues to find perceived benefit in their use. The market for supplements has now ballooned to nearly $50 billion annually. This perennial trend upward comes despite increasing scrutiny on the safety and efficacy of dietary supplements based on numbers of emergency room visits attributed to supplement usage and analyses of the literature suggesting limited benefit. Under current regulatory guidelines, limited safety and efficacy data are required for marketed supplements prior to them hitting the store shelves. National Center for Complementary and Integrative Health (NCCIH) supports a broad portfolio of research on a wide variety of natural products, including many well-known dietary supplements. NCCIH includes in the term "natural products" substances produced by plants, microbes, and other living organisms. We also include probiotics in this category. Many of these natural products are also sold as dietary supplements. The term "dietary supplement" was created specifically by the Dietary Supplement Health and Education Act in 1994. The law defines dietary supplements in part as products taken by mouth that contain a "dietary ingredient." Dietary ingredients include vitamins, minerals, amino acids, and herbs or botanicals as well as other substances that can be used to supplement the diet. One of the key motivations for NCCIH investment is creation of rigorous data on the safety and efficacy of supplements such that consumers and healthcare professionals can make informed decisions about their usefulness. During its 20-year existence, NCCIH has funded several large efficacy studies on dietary supplements (Hopp, 2015). In general, these large trials were based on smaller published studies that suggested efficacy. To date, nearly all of these large trials have failed to replicate the anticipated benefits of the products. These trials were questioned and criticized after publication by those who felt suboptimal choices were made for various aspects of the study design, including dose (Blumenthal and Farnsworth, 2005), formulation (Hochberg, 2006), and patient population (Eells et al., 2011). Retrospective analysis of these trials by NCCIH determined that additional preliminary clinical research could have been completed to optimize the study design before launching the larger study. Based on the lessons learned, NCCIH has made numerous changes in its approach to funding clinical research on dietary supplements. These include closer scrutiny of both the products used and the trial design elements to build an evidence base that allows for the conduct of a definitive efficacy trial.

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Product Integrity

There are currently tens of thousands of dietary supplements on the market (https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-agencys-new-efforts-strengthen-regulation-dietary). Even for products that are nominally the same, there are countless different brands and formulations available. The botanical turmeric is a particularly noteworthy example. There has

ABBREVIATIONS: FOA, funding opportunity announcement; NaPDI, Natural Product Drug Interaction Research; NCCIH, National Center for Complementary and Integrative Health; NIH, National Institutes of Health; PK, pharmacokinetics.

been abundant research on this plant and its constituents. There are also a wide range of health claims attached to it (Nelson et al., 2017). Powdered raw turmeric root and a variety of root extracts are available. Different solvents may be used for the extraction. The extracts may undergo further processing to increase the concentrations of curcuminoids, the purported active ingredients in turmeric. The product can be formulated as a tincture, a tea, a capsule, or a tablet. A wide variety of excipients with varying concentrations can be added. Special formulations may incorporate nanoparticles or phytosomes for the explicit purpose of increasing bioavailability of the ingredients (Marczylo et al., 2007). The complexities become almost infinite when multiple natural products are mixed to form combination products. These products are frequently labeled as proprietary blends, making it difficult, if not impossible, to know exactly the identity and concentration of all components. In all these examples, the final composition of the "turmeric" product will be different, and/or the product might be absorbed, distributed, or metabolized differently when consumed.

This heterogeneity is difficult enough to manage under best-case scenarios. Unfortunately, it is well-established at this point that what is on the label of a dietary supplement does not always match what is in the bottle. There are numerous reports of products that contained dramatically more or less of the ingredients relative to what is listed (Gurley et al., 2020). More troubling are examples of products adulterated with substances not mentioned at all on the label. Some of these might be innocent or unintended mistakes, but some demonstrate a clear intention to spike supplements with pharmaceutical ingredients (Vaclavik et al., 2014). Although this represents only a small fraction of the overall supplement marketplace, these situations still are uncovered with disturbing frequency. The consequences of such adulteration can be dire (Geller et al., 2015).

A researcher needs to be cognizant of these realities before initiating a project involving commercially sourced dietary supplements. It is not a stretch to say that no two products are the same. Therefore, it is incumbent on the researcher to know with enough detail the composition of the product they are using. Fifteen years ago, NCCIH created the Product Integrity Policy (https://www.nccih.nih.gov/research/nccih-policy-natural-product-integrity) so that NCCIH and our funded investigators could have confidence that the products used in NCCIH-funded research are well-characterized, and therefore, the eventual results could be properly interpreted, accurately compared with other studies on similar products, and confidently replicated if necessary. Although the principles of the Product Integrity Policy are held sacrosanct at NCCIH, the implementation of the policy takes a much more pragmatic and flexible approach. The information requested is tiered based on the type of product involved (complex product, refined product, probiotic) and stage of research (in vitro, animal, human). Furthermore, there are no predetermined methodologies required for product characterization. This again depends on what is reasonable for the specific product, the type of project, and the resources available. In all cases, NCCIH works closely with the applicant in an iterative fashion until sufficient product characterization is achieved.

Clinical Trial Design

In 2015, NCCIH issued a set of funding opportunity announcements (FOAs) to call for early-phase natural products clinical research, and NCCIH has continued to have this type of FOA available. The goal of these FOAs was to support the early and midphase clinical trials that are necessary to plan a well-designed efficacy trial. The preliminary data gathered in these earlier studies are the essential building blocks for natural product clinical efficacy trials (Fig. 1). Analogous to pharmaceutical development, clinical research on natural products works best when it proceeds in a stepwise fashion. Researchers need to understand

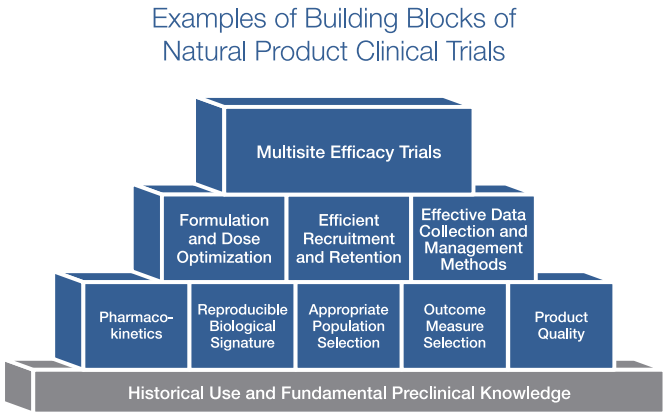

Fig. 1. Examples of building blocks for NCCIH-funded natural products clinical trials.

the pharmacokinetics (PK) of the natural product if absorption is necessary for its biologic activity. Studying the PK of botanicals is more complicated because of the numerous chemical constituents within a botanical extract (Shipkowski et al., 2018), and new methods for examining polypharmacokentics have been developed to examine the impact of multiple constituents (Li et al., 2018). If the active constituents with the botanical are unknown, additional preclinical work may be needed before PK studies can be conducted. Once PK information is available, investigators can determine the optimal frequency of daily dosing. Before conducting an efficacy trial, additional data are needed to ensure that the investigators have selected an appropriate population that is likely to respond to the natural product and that the outcome measure selected will be responsive to change. As noted above, the quality and consistency of the product are critically important.

For NCCIH, another key element of preliminary data is that investigators propose a way to measure the effect of the natural product on a *biologic signature* when the natural product is used by humans. This biologic signature should be a measure of the postulated mechanism of action by which the natural product might ultimately modify the clinical condition or symptom(s) of interest. Biologic signatures may be biologically based mechanisms or behavioral processes, such as an objective single measure, proxy, correlate, or combination of molecular/cellular, psychologic, neural circuit, tissue/organ, and/or somatic changes. Applicants to these FOAs are asked to identify a priori the specific biologic signature(s) and define how much of a change will be detected and why that amount of change is clinically relevant. A critical part of measuring the impact on a biologic signature is demonstrating that the effect can be reproduced in a second trial. The dose of the natural product can be optimized to have the maximal impact on the reproducible biologic signature. One example of a drug derived from a dietary supplement is icosapent ethyl (Vascepa), which initially was studied for impact on elevated triglycerides (biologic signature) in two studies and is now approved as an adjunctive therapy to reduce risks of cardiovascular events (clinical outcome) in individuals with high triglycerides (Bhatt et al., 2019).

Including a reproducible biologic signature in the efficacy trial makes the results of the efficacy trial more informative. Absent a biologic signature, there are three possible outcomes in an efficacy trial: 1) the intervention demonstrates efficacy (it works, and we do not know why); 2) inability to detect benefit (it did not work, and we do not know why); and 3) the intervention worsens the clinical outcome (it causes harm, and we do not know why). If we include the reproducible biologic signature in the efficacy trial, we also learn the following: 1) when the intervention improves the clinical outcome, the trial may have also identified

a biologic signature that is the mediator of that effect, which could become the target for future treatment development; 2) when the results do not demonstrate benefit or harm, the biologic signature is not a useful target to pursue for that condition; and 3) when the trial results demonstrate worsening of the condition, the biologic signature may be a mediator of worsening outcome, which would need further study to determine whether it is a useful to target as a mechanism to block for future treatment development. Thus, NCCIH has concluded that whenever possible, efficacy trials should include a reproducible biologic signature. It is recognized that there are some specific situations in which it is impractical or impossible to measure a potential biologic signature of the natural product, and yet there are substantial other preliminary data to warrant an efficacy trial. At all times, the current level of evidence for a specific natural product must be evaluated to determine the most appropriate clinical trial to pursue next.

NCCIH Investment

NCCIH maintains a robust and diverse portfolio of investments in natural products research. This portfolio includes both preclinical and clinical studies. Those interested in learning more about what specific projects are supported by NCCIH and all of NIH are encouraged to use the NIH Research Portfolio Online Reporting Tools Expenditures and Results (RePORTER) data base (https://projectreporter.nih.gov/). In addition to the set of investigator-initiated FOAs described above, there are a few major programs at NCCIH worth mentioning specifically.

One of these is the Botanical Dietary Supplement Research Centers that are funded and managed in close collaboration with the NIH Office of Dietary Supplements. This is a longstanding program that seeks to gain in-depth knowledge about the biologic effects of selected natural products. The next cohort of centers will be funded in the summer of 2020 (https://grants.nih.gov/grants/guide/rfa-files/rfa-od-19-001.html). The explicit focus of the centers in this cycle is development of data that will help in the design of a maximally informative clinical trial. Consistent with NCCIH thinking regarding clinical trial design, this includes establishing which components of these complex mixtures are responsible for specific activities, understanding the mechanisms of those activities, and demonstrating clear metrics of bioavailability for those components.

A second major program supported by NCCIH is the Natural Product Drug Interaction Research (NaPDI) Center. Initiated 5 years ago, this center is charged with conducting rigorous research on a select number of natural products regarding their potential as perpetrators of clinically relevant PK interactions with other medications. Interactions involving St. John's wort and grapefruit juice are well-established, but there are many other natural products in which the science is not so clear (Gurley, 2012; Gurley et al., 2012). The center is also charged with developing recommended approaches to guide the research community on how best to design drug interaction studies involving complex mixtures. These recommendations are intended to adapt the established Food and Drug Administration guidance (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/vitro-drug-interaction-studies-cytochrome-p450-enzyme-and-transporter-mediated-drug-interactions) for drug-drug interaction studies to accommodate the unique requirements of working with complex botanical products. This investment is also being renewed (https://grants.nih.gov/grants/guide/rfa-files/rfa-at-20-002.html) in 2020 to continue developing the knowledge base around the PK of selected natural products. As a companion to the NaPDI Center, NCCIH is also supporting an R21 effort (https://grants.nih.gov/grants/guide/rfa-files/RFA-AT-20-001.html), which will support investigation of a broader array of natural products for their ability to influence the PK of various medications through interaction with drug-metabolizing enzymes and transporters. Importantly, as part of the NaPDI Center, NCCIH is also supporting development of a data repository (https://repo.napdi.org/) that will contain data generated by both the center and the associated R21 projects. The hope is that this repository will allow for generation of new hypotheses regarding which natural products warrant additional clinical studies to identify the mechanism and magnitude of any interactions.

Conclusion

NCCIH has funded numerous clinical trials on a wide variety of natural products and dietary supplements over our 20-year history. Shaped by that experience, we have developed a continuum of research on natural products, with FOAs to support mechanistic, preclinical, and clinical trials. This has been coupled with a rigorous process for characterizing the products used in those studies. There has been a deliberate effort to provide FOAs along the pipeline of research for testing the efficacy of natural products after sufficient preliminary data have been collected to allow a well-informed study design. Specific gap areas have been addressed by the development of special programs, such as the Botanical Research Centers and the NaPDI Center. As we move forward, NCCIH will continue to build the evidence base around natural products to allow consumers and healthcare practitioners to make informed decisions regarding their usefulness.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Hopp, Weber.

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