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Review

Similarities and important distinctions between drug and behavioral intervention development

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Abstract
There has been a proliferation in behavioral intervention development due to guidelines recommending their use for managing common, distressing, and interfering symptoms (e.g., insomnia, pain, fatigue) resulting from medical disease (e.g., cancer) and its treatment. Several models of behavioral intervention development exist (e.g., Stage Model, ORBIT). In this review, we focus on the National Institute of Health (NIH) Stage Model for Behavioral Intervention Development because it offers the closest analogue to the formalized drug development process. This review compares the phases of drug development to the six stages of the Stage Model for behavioral intervention development to assist investigators in understanding similarities and differences in terminology (i.e., *Phase* versus *Stage*), study designs and methods, and ultimate purpose. Distinguishing features of the NIH Stage Model for behavioral intervention development are highlighted and include: (1) a recursive and iterative flow; and (2) a focus on intervention mechanisms at every stage of development. To illustrate each stage, we refer to a program of research developing and testing a behavioral insomnia and symptom (e.g., pain, fatigue) management intervention for patients with life-threatening hematologic cancer. This illustrative example conveys the initial steps required to develop and pilot test a behavioral intervention before progressing to larger-scale efficacy and effectiveness testing. To conclude, we offer recommendations for investigators designing and testing behavioral interventions. Recommendations are first, develop a long-term research plan that begins with the end in mind, and second, ensure each step in the research plan provides sufficient information to proceed to the next stage.

Keywords Behavioral intervention development · Drug development · Stage model · Insomnia · Behavioral symptom management · Hematologic cancer

1 Introduction

Behavioral interventions teach behavioral, non-pharmacological strategies to manage health [1]. For many physical health conditions (e.g., cancer, chronic pain), behavioral interventions (e.g., Cognitive-Behavioral Therapy for Insomnia; Pain Coping Skills Training) are efficacious and recommended for distressing symptoms, such as insomnia, pain, and fatigue resulting from the disease and its treatment [2–5]. Given this, there has been a proliferation in behavioral intervention development for specific health conditions and symptoms.

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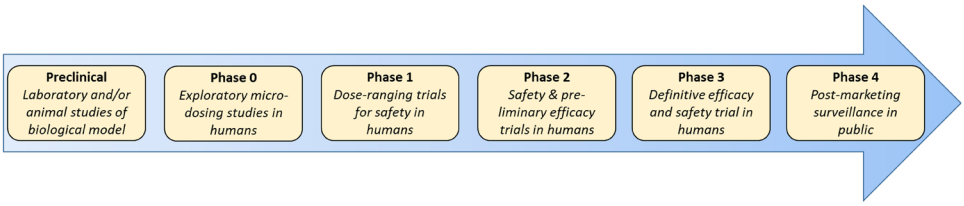

Fig. 1 Drug development process (Figure adapted from Ciociola et al. [8])

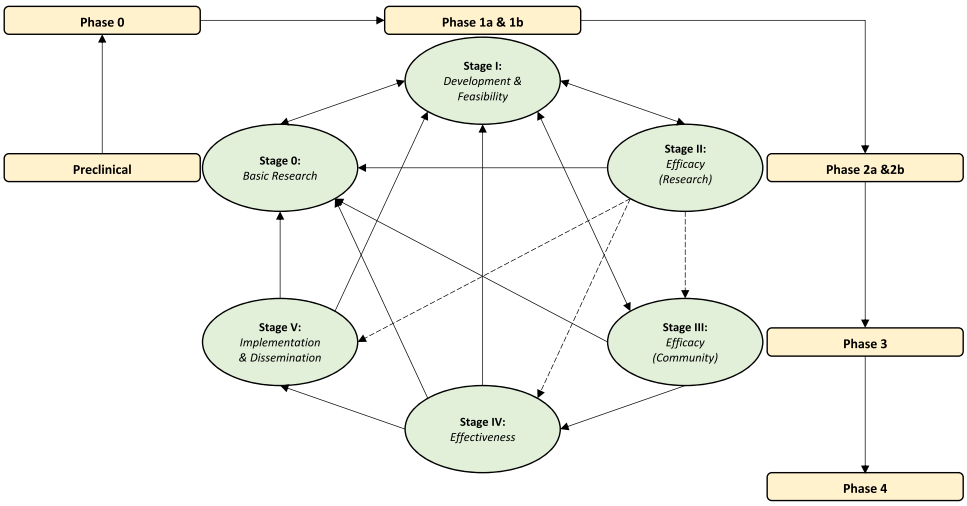

Fig. 2 NIH stage model with drug development phases (yellow boxes indicate drug development process. Green boxes indicate NIH Stage Model adapted from Onken et al. [6]. Dotted lines indicate caution when considering this pathway

Behavioral intervention development (e.g., Stage Model [6], ORBIT [7]) is both similar to, and different from, the formalized drug development process (Fig. 1; [8]). Several models of behavioral intervention development exist (e.g., Stage Model, ORBIT). Each model has unique strengths and applications. In this review, we focus on the National Institute of Health (NIH) Stage Model for Behavioral Intervention Development because it offers the closest analogue to the formalized drug development process [5]. The NIH Stage Model outlines six stages of behavioral intervention development that largely align with new drug development (Fig. 2), though progression through these stages is distinct. Drug development is linear with an orderly advancement through phases. Conversely, there is much back and forth between the recursive stages of behavioral intervention development. A return to an earlier stage is possible after any subsequent stage, if warranted by qualitative or quantitative data. Additionally, behavioral researchers are encouraged to examine intervention mechanisms at every stage, whereas the biological model for a new drug is finalized during *Preclinical* and *Phase 0* work. Still, the overall goal of drug and behavioral intervention development is similar—to produce a highly potent and implementable intervention that can improve physical and/or mental health [6–9].

Here, we review and compare study designs and methods for developing behavioral interventions with research evaluating new drugs to help investigators distinguish their similar terminology and ultimate purpose. To illustrate the unique features of each stage of behavioral intervention development, we refer to a line of research developing and testing a behavioral insomnia and symptom management (e.g., pain, fatigue) intervention for patients with life-threatening hematologic cancer (Table 1). This illustrative example conveys the initial steps required to develop and pilot test a behavioral intervention before progressing to larger-scale efficacy, effectiveness, and implementation testing. To conclude, we offer recommendations for researchers designing and testing behavioral interventions.

Table 1 Key characteristics of illustrative example of behavioral intervention development

Stage	Primary aim(s)	Setting	Method	Primary outcome(s)
0	• Identification of target population and intervention • Identification of conceptual and theoretical models	Research	• Clinical observation • Literature review	• Population (i.e., hematologic cancer) • Intervention (i.e., MBTI) • Spielman 3-P Model of Insomnia • Metacognitive Model of Insomnia
Ia	• Development • Adaptation	Research	• Patient, clinician focus groups • User testing	• Hematologic cancer symptom experience • Intervention content • Intervention format (e.g., session number, length, delivery, materials etc.)
Ib	• Feasibility • Acceptability	Research	• Single-arm pilot • Small RCT	• Feasibility (i.e., accrual, attrition, adherence) • Acceptability
II	Efficacy	Research	RCT	Insomnia symptom severity
III	Efficacy	Community	RCT	Insomnia symptom severity
IV	• Effectiveness • Cost-Effectiveness	Community	RCT	• Health-related quality of life • Insomnia symptom severity • Survival • Cost
V	• Implementation intervention/strategies • Dissemination	Community	RCT	• Intervention uptake • Intervention implementation • Health-related quality of life

MBTI Mindfulness-based therapy for insomnia, *RCT* randomized controlled trial

2 Methods

2.1 Preclinical phase for drugs/Stage 0 for behavioral interventions

2.1.1 Goal

The goal is to identify a promising drug compound or behavioral intervention to be further developed and tested.

2.1.2 Description

Drugs are informed by biological models. The biological basis for a cancer drug might be that the cancer grows by downregulating a certain protein. The candidate compound would therefore be one which selectively upregulates that same protein. The *Preclinical* phase of drug development begins in cell cultures or animal models where wide-ranging doses of the candidate compound provide increasingly realistic approximations of performance in humans (i.e., pharmacokinetics; [10–12]). The *Preclinical* phase may require years of laboratory experiments to adjust the complex biological model [13]. However, once this work is done, the biological justification for a candidate compound is essentially complete. Subsequent testing does not assess the biological model itself, but rather the efficacy of the investigational drug based on that model.

Stage 0 for behavioral interventions explores the need for a behavioral intervention and for whom, as well as why and how an intervention might produce change [6, 9]. Behavioral researchers may reference animal models like those used for drug development, but more typically rely on identification of a clinical problem, assessment of literature, and/or observational analyses in humans to answer these preliminary questions. Similar to *Phase 0* for drug development, a focus of *Stage 0* is identifying change models. However, behavioral interventions are unique in their basis on both: (1) a conceptual model that provides the "why" an intervention might work; and (2) an intervention model that provides the "how" an intervention might work through a specific casual pathway [6, 14]. Conceptual and intervention models are not as self-evident as biological models for drugs, and the science of behavioral intervention development prioritizes ongoing theoretical justification beyond *Stage 0* [6].

2.2 Phase 0 for drugs

2.2.1 Goal

The goal of a *Phase 0* study is to verify whether the investigational drug behaves in humans as expected from *Preclinical* data. There is no analogue for behavioral interventions.

2.2.2 Description

An exploratory micro-dosing study (e.g., 10–15 participants) estimates the pharmacokinetic curve for drug doses that are too small to be of clinical significance [11–13]. The pharmacokinetic curve should rise or fall as predicted by the biological model. *Phase 0* studies can be used to rank drug compounds, with those demonstrating the best pharmacokinetic properties advancing for more testing [15, 16]. Not all new drugs require a *Phase 0* study.

2.3 Phase 1 for drugs/Stage I for behavioral interventions

2.3.1 Goal

The goal of a *Phase 1* drug trial is to find an optimal dose (and sometimes dosing schedule), which is defined as the maximum dose without unacceptable side effects [10–12]. The goal of a *Stage I* behavioral intervention trial is to develop an intervention that can be delivered safely and reliably reproduced for further testing [6, 9]. This initial version of the intervention is not optimized, and modification is likely in later stages.

2.3.2 Description

Phase 1 drug trials focus on pharmacokinetics and safety in small samples (e.g., 20–100 healthy participants; [8]). Participants are given the smallest dose of the drug (*Phase 1a*), or multiple doses (*Phase 1b*), consistent with *Preclinical* and *Phase 0* work [8, 10–12]. If no adverse events are observed, the dose is slowly escalated until an unacceptable rate of adverse events is discovered [16]. For most drugs it is assumed that a larger dose yields a larger benefit, thus the ideal dose is just below the threshold for too many adverse events (i.e., maximum tolerated dose; [16]).

Stage I for behavioral interventions involves developing or adapting a sufficiently detailed intervention protocol (*Stage Ia*) before preliminary testing (*Stage Ib*). *Stage Ia* typically entails qualitative interviews or focus groups with relevant individuals (e.g., patients, clinicians) to obtain an initial assessment of intervention models, format, delivery, and content [6]. It is possible that patients or clinicians conceptualize the problem inconsistently with proposed models, and/or suggest changes to the intervention protocol. If so, more *Stage 0* and *Stage 1* work is warranted.

Like *Phase I* for a new drug, *Stage Ib* generally begins with small-scale testing using a single-arm, feasibility trial to test whether the intervention protocol is feasible, acceptable, and can be delivered with adequate fidelity and safety based on pre-specified benchmarks. This remains development work rather than a formal assessment, therefore sample sizes only need to be large enough to answer the question of whether the behavioral intervention seems plausible (e.g., 20–30 participants; [6, 14]). Outcomes should be evaluated with discretion since estimates from a small, uncontrolled sample will lack precision. If a study fails to meet a benchmark but the researcher discovers how to address the problem that represents progress [14, 17]. Next, researchers might extend early proof-of-concept work by testing a promising behavioral intervention using a randomized design. Samples sizes remain modest (e.g., 60–80 participants), thus aims primarily assess the feasibility, acceptability, and safety of performing a *Stage II* efficacy trial (e.g., participants can be identified, randomized, etc.), and secondarily as providing data about intervention effects [6, 14, 17].

2.4 Phase 2 for drugs/Stage II for behavioral interventions

2.4.1 Goal

The goal of a *Phase 2* drug trial is to provide sufficient evidence (i.e., safety, preliminary efficacy) to confidently and ethically proceed to a definitive *Phase 3* efficacy trial. For behavioral interventions, the goal of *Stage II* is efficacy testing in the research setting.

2.4.2 Description

Phase 2a drug trials assess safety in humans without a control group, while *Phase 2b* trials assess safety, feasibility, and preliminary efficacy in humans relative to a control [8]. There will not be enough participants at the maximum tolerated dose (MTD) in *Phase I* to assess biological activity or safety with full confidence. Thus, the MTD might be reconsidered during *Phase 2a*. Sample sizes are approximately 50–100 participants with the disease of interest (e.g., cancer), and are based on the desired precision for safety parameters (e.g., proportion of patients with serious bleeding; [10–12]). *Phase 2b* drug trials add a control and seek to provide information about safety, feasibility (e.g., recruitment and retention goals can be met, high quality data can be collected), and preliminary efficacy that justifies proceeding to a more time-consuming and costly *Phase 3* trial [11, 12, 16]. Statistical significance will still be lacking but overall patterns of findings can help the researcher anticipate results from a larger *Phase 3* trial.

Stage II involves randomized assessment of efficacy for a behavioral intervention in the research setting with research-based clinicians [6, 9]. Unlike *Phase II* for drug development, a *Stage II* trial is fully powered (e.g., 100–400 participants) to detect a minimum clinically important difference in the primary outcome [6]. Much thought is given to the control condition, which should be sufficiently similar (e.g., dose, timing of attention) but not too similar in content to the intervention [18]. Another key consideration is inclusion criteria. When the target population is broadly defined, external validity increases but effect size decreases; conversely, a more defined population increases internal validity, yielding a stronger effect size. Researchers prioritize internal validity during *Stage II* to maximize intervention effect [6, 9].

2.5 Phase 3 for drugs/Stage III for behavioral interventions

2.5.1 Goal

The goal of a *Phase 3* drug trial is definitive assessment of efficacy and safety. A *Stage III* behavioral intervention trial examines intervention efficacy in the community.

2.5.2 Description

Phase 3 drug trials evaluate efficacy in humans compared to the current standard of treatment [11, 12]. Sample size for a *Phase 3* trial depends on the condition under study, though is usually large (e.g., 300–3000 participants; [8]). Two successful *Phase 3* trials are typically required for regulatory approval, but trials can continue while approval is pending to allow patients to receive a possibly lifesaving drug until it can be purchased [16].

Much like *Phase III* for drug development, *Stage III* for behavioral interventions extends large-scale (e.g., 200–700 participants) efficacy testing to the community [6, 9]. Examination of intervention mechanisms continues to be integral, and trials might also explore specific intervention components and/or theory-driven moderators [6]. Internal validity remains high since the intervention is tested in a tightly controlled community setting with community-based clinicians. Clinician training and fidelity monitoring should be formally integrated and assessed to prepare for an effectiveness trial where external validity becomes the priority [6, 19]. Unless early work is conducted in the community, a return to *Stage I* to adapt the intervention for community-based participants and clinicians is likely necessary before a *Stage III* trial.

2.6 Phase 4 for drugs/Stage IV for behavioral interventions

2.6.1 Goal

The final phase of drug development is a *Phase 4* trial, which seeks to assess the long-term safety and real world effectiveness of a new drug after it receives regulatory approval (i.e., post-marketing surveillance; [8]). The goal of a *Stage IV* behavioral intervention trial is to examine the effectiveness of an efficacious behavioral intervention.

2.6.2 Description

Phase 4 drug trials may be required by regulatory agencies or can be voluntarily undertaken by sponsoring companies to explore potential long-term drug benefits/harms, comparative effectiveness with other marketed drugs, and/or indications for special populations (e.g., pregnant women; [11, 12, 16]). Observational datasets with thousands of individuals who have taken the drug are often used to complete this work [11, 12, 16].

Stage IV for behavioral intervention development diverges from *Phase 4* for new drugs. Behavioral researchers in *Stage IV* aim to maximize external validity by evaluating the effectiveness of a behavioral intervention in a community setting against the current standard of care [6, 20]. Inclusion criteria for a *Stage IV* trial are broadly defined and participants (e.g., 300–1000) are treated as they would when the intervention is prescribed in the real world [20]. Ideally, no features of the study should increase compliance beyond what routinely occurs in clinical practice [20]. *Stage IV* outcomes are more generally applicable than efficacy trials (e.g., quality of life, survival), since researchers are now interested in whether the intervention has a broad, long-term effect on the target population [6].

2.7 Stage V for behavioral interventions

2.7.1 Goal

Stage V aims to assess implementation of an effective behavioral intervention in community settings [6]. There is no analogue for drug trials.

2.7.2 Description

Once a behavioral intervention has proven effective, implementation research examines adoption of that intervention by clinicians and/or healthcare systems [21]. In a *Stage V* trial, what is tested is not the behavioral intervention itself but rather a specific implementation intervention (e.g., electronic clinical reminder) or grouping of interventions (i.e., implementation strategy) designed to enhance uptake of the intervention into routine and sustained clinical use [21]. The typical unit of randomization and analysis is the clinician or healthcare system, and outcomes are focused on behaviors such as rates of adoption of the behavioral intervention [21].

3 Results

3.1 Illustrative example of behavioral intervention development

3.1.1 Stage 0

Behavioral interventions have been successful in treating insomnia in general and cancer populations [4, 22]; however, there is increasing recognition that current interventions must be adapted to better meet the needs of those with cancer [23]. Hematologic cancer patients, in particular, report high rates of insomnia [24–27]. Insomnia symptoms faced by patients with hematologic cancer are best conceptualized using the Spielman 3-P Conceptual Model of Insomnia [28]. The Spielman 3-P Conceptual Model of Insomnia describes how insomnia symptoms emerge and

progress from acute to chronic insomnia, with an emphasis on biopsychosocial predisposing, precipitating, and perpetuating factors [28].

Hematologic cancer patients are distressed due to their disease, *predisposing* them to poor sleep [24, 29–31]. Additionally, some patients may have experienced disrupted sleep prior to diagnosis, and/or may have other predisposing risk factors (e.g., female sex, hyperarousability). Once hospitalized for treatment, patients experience a challenging inpatient environment that *precipitates* a sleep disturbance [32–34]. Lack of sleep and distress related to lack of sleep can lead to unhelpful behaviors (e.g., inconsistent sleep schedule, extending time in bed, sleep medication use) and thoughts that *perpetuate* insomnia symptoms and worsen pain, fatigue, and distress, which further interfere with sleep [23, 28, 35].

Based on the Metacognitive Model of Insomnia [36], Mindfulness-Based Therapy for Insomnia (MBTI) is a group-based, behavioral intervention that combines sleep consolidation and sleep reconditioning with training in mindfulness principles and meditations [35]. This mindfulness-based behavioral protocol emphasizes non-judgmental, present-moment awareness and acceptance of insomnia symptoms, and disruptive thoughts related to poor sleep. This approach is well-suited to the challenging and uncontrollable treatment and symptom demands faced by hematologic cancer patients. Together, mindfulness meditations and behavioral insomnia strategies address key predisposing (e.g., distress), precipitating (e.g., inpatient treatment), and perpetuating (e.g., inconsistent sleep schedule, extending time in bed, sleep medication use) factors contributing to insomnia symptoms.

3.1.2 Stage I

Treatment for hematologic cancer is time-intensive and results in immunosuppression. In addition to insomnia, hematologic cancer patients report numerous severe and concurrent symptoms throughout treatment, such as pain, fatigue, and distress [24–27]. To better meet the needs of these patients, MBTI must be adapted for individual and remote delivery for better flexibility around ongoing treatment. There is no mindfulness-based behavioral intervention for hematologic cancer patients that systematically addresses insomnia, *as well as* pain, fatigue, and distress. An adapted MBTI protocol for this population should provide targeted training in evidence-based behavioral skills to cope with pain, fatigue, and distress symptoms and their interference to sleep quality.

In *Stage 1a* (see Table 1), researchers conduct three patient (N = 3–6/group) and one clinician (N = 6) focus groups to evaluate the adapted MBTI protocol (Nite2Day). Interview guides query participants on proposed intervention content and format. Qualitative findings inform intervention refinement, for example: 1) behavioral skills (e.g., activity rest pacing, pleasant activity planning) are added to address pain, fatigue, and distress; and 2) due to recurrent hospitalizations, recommendations are added for using intervention strategies while inpatient.

Researchers examine Nite2Day feasibility and acceptability in a single-arm pilot (*Stage Ib*). Eligible hematologic cancer patients are: (1) ≤ 8 weeks post-discharge from inpatient treatment, and (2) reporting at least Subthreshold/Mild insomnia symptoms across the past 2 weeks on the Insomnia Severity Index [37]. Nite2Day is delivered by a PhD-level clinical psychologist. Feasibility is quantified by accrual (N = 30/15 months), attrition (≤ 20% at post-intervention), and adherence (≥ 80% completing all assessments, sessions). Acceptability benchmark is ≥ 80% of participants reporting intervention satisfaction ($M \geq 3.00/4.00$) at post-intervention [38]. Sessions are audio-recorded and a random sample of 10% is evaluated by an independent research coordinator. Self-report measures are collected at baseline, post-, and 1-month post-intervention to explore changes in primary (insomnia symptom severity) and secondary (pain, fatigue, distress, mindfulness, symptom management self-efficacy) outcomes. As recommended for feasibility pilots, *p*-values are not reported and effect sizes are exploratory [17, 39, 40].

Researchers then conduct a small, randomized pilot of Nite2Day (*Stage Ib*). Hematologic cancer patients (N = 60) ≤ 8 weeks post-discharge from inpatient treatment reporting at least Subthreshold/Mild insomnia symptoms are randomized to Nite2Day or Usual Care. Primary aim remains assessment of feasibility with a priori benchmarks based on the literature [41–43] and prior *Stage I* work: (a) study accrual (N = 60/24 months); (b) attrition (≤ 25% at post-intervention); and (c) engagement (≥ 75% completing all assessments, sessions, and reporting use of coping skills). Self-report measures are collected at baseline, 8-, and 12-week follow-up. Formal tests of between-group differences are not conducted [17]. Instead, effect sizes and 95% confidence intervals are calculated, with moderate-to-large effect sizes (Cohen's $d > 0.50$) considered noteworthy [39, 40]. Promising qualitative feedback and feasibility, acceptability, and pre-post data from pilot trials suggest readiness for a larger, fully powered efficacy trial.

3.1.3 Stage II

Researchers conduct an efficacy trial randomizing hematologic cancer patients (N = 160) ≤ 8 weeks post-discharge from inpatient treatment reporting at least Subthreshold/Mild insomnia symptoms to Nite2Day or an attention-matched, health education control. The primary aim is to determine efficacy of Nite2Day for reducing insomnia symptom severity by a minimum clinically important difference (i.e., 6 points on Insomnia Severity Index; [44]). Mean difference from baseline to 8-week follow-up is reported with a *p*-value and 95% confidence interval. Efficacy is demonstrated if Nite2Day results in a statistically significant, clinically meaningful reduction in insomnia symptom severity compared to the control. Researchers also explore the efficacy of Nite2Day for improving secondary outcomes (i.e., pain, fatigue, distress, mindfulness, symptom management self-efficacy) at 8-weeks, and maintenance of effects at 12-weeks. An exploratory aim assesses mindfulness as a mediator of intervention effects. Results of mediation analyses are used to refine the Nite2Day conceptual model and guide future assessment of intervention mechanisms (e.g., mindfulness, symptom management self-efficacy). Once efficacy is demonstrated in a controlled research setting, a *Stage III* trial evaluates efficacy in the community.

3.1.4 Stage III

Prior to a *Stage III* trial, researchers conduct additional *Stage Ia* work (i.e., patient, clinician interviews) to adapt Nite2Day for hematologic cancer patients at a community-based cancer center. The adapted Nite2Day protocol, delivered by a nurse practitioner, is pilot tested against an attention-matched, heath education control in a small, randomized trial (N = 60) at a community-based cancer center (*Stage Ib*). Nurse practitioners are trained and audio-record mock sessions to be certified for intervention delivery and thereafter attend ongoing supervision. Researchers then conduct a large (e.g., 250 participants) *Stage III* efficacy trial in the same setting, using the same procedures as previous *Stage I* and *II* work. Aims are similar to prior efficacy testing with an exploratory aim to examine potential moderators (e.g., participant sex, race) of intervention effects. If the intervention can be delivered with fidelity in the community without losing efficacy, chances of a successful *Stage IV* effectiveness trial are improved.

3.1.5 Stage IV

Researchers conduct a multi-site effectiveness trial randomizing hematologic cancer patient (N = 350) ≤ 8 weeks post-discharge from inpatient treatment to Nite2Day or Usual Care. Eligibility is determined based on report of a sleep complaint and clinical variables (e.g., diagnosis, treatment) in the electronic medical record (EMR). Nite2Day is delivered by trained nurse practitioners. Participants complete self-report measures through the EMR on health-related quality of life and symptoms (e.g., insomnia) at baseline, 6-, and 12-month post-intervention. Disease-free survival and overall survival intervals are collected by EMR review. Effectiveness of Nite2Day is demonstrated by larger effect on health-related quality of life (primary outcome), symptoms, and survival intervals compared to Usual Care at 6- and 12-month follow-up. Researchers conduct an economic evaluation of Nite2Day to determine its cost-effectiveness. Nurse practitioners and study staff complete exit interviews to obtain qualitative data on barriers and facilitators to future implementation of Nite2Day.

3.1.6 Stage V

Researchers conduct a two-arm, cluster randomized trial comparing two implementation strategies among National Cancer Institute Community Oncology Research Program practice clusters [45]. Three cohorts (n = 16) of practice clusters (15–25 participants/cluster) will be randomized to study arms testing separate implementation strategies. The primary outcome (patient level) is Nite2Day uptake (i.e., proportion of participants completing all sessions in 8 weeks). Secondary outcome (practice cluster level) is program implementation, measured by the General Organizational Index (GOI; [46]) at baseline, 6- and 12-month post-intervention. The GOI measures factors (e.g., participant identification, process monitoring etc.) that influence implementation of evidence-based practices [46]. An exploratory aim assesses patient health-related quality of life at baseline, 6- and 12-month assessments.

4 Discussion

Unlike other models for behavioral intervention development (e.g., ORBIT [7]), the NIH Stage Model [6] creates a similar language to drug development. Researchers will encounter terminology from drug development (e.g., *Phase 1*, *Phase 2*) when working on interdisciplinary teams, and should be able to translate that terminology into the functional equivalent within their discipline. Yet, the literature lacks a concise review comparing study design and methods for *phases* of drug development and *stages* of behavioral intervention development (see Fig. 2) that clarifies similarities and distinctions, and uses an illustrative example to underscore key features (see Table 1).

We highlight that *Phase 3* efficacy trials for a new drug and *Stage II* and *III* efficacy trials for a promising behavioral intervention are the lynchpin of both processes, with all preceding work building toward that point, and subsequent research beginning under the premise that the drug or behavioral intervention is efficacious. Indeed, *Phase 3/Stage II* and *III* is when the design and methods of drug and behavioral intervention trials are most similar. Following models from drug development, novel use of adaptive designs is becoming increasingly common in *Stage II* and *III* behavioral intervention efficacy trials [47]. Adaptive designs can accommodate early results that suggest treatment benefit, or lack thereof, thus warranting change in sample size, treatment dose, or possibly trial termination [47, 48]. There are calls for more widespread use of adaptive designs to increase efficiency and enhance progress towards effectiveness and implementation research for behavioral interventions [19, 49].

A defining feature of the NIH Stage Model distinguishing it from drug development is its ongoing emphasis on mechanisms. Understanding mechanisms of action behind a behavioral intervention is initially explored during *Stage 0* and *I* but should continue in subsequent stages. This differs from drug development where the biological model is determined in *Preclinical* work and *Phase 0*. There is no analogue for *Phase 0* in behavioral intervention development, further underscoring that justification for a new drug's biological model is isolated to, and prioritized in, early phase research. For behavioral intervention development, ongoing assessment of mechanisms across all stages has highly pragmatic implications by helping to: (1) boost effects; and (2) streamline an intervention to its essential components to cut costs and improve implementation in healthcare systems, the ultimate goal for behavioral intervention researchers.

Another unique characteristic of the NIH Stage Model is that it does not require the research to be done in a specified order, as is the case for drug development. For instance, depending upon intervention qualities, *Stage I* may lead to *Stage II*, or directly to *Stage III* (e.g., if *Stage I* was conducted in the community). It is equally plausible that *Stage II*, *III*, or *IV* will lead to further *Stage I* modification of the intervention. Notably, behavioral intervention researchers have started using hybrid designs wherein *Stage III* efficacy and *Stage IV* effectiveness trials might be combined. Similarly, *Stage IV* and *Stage V* trials can also be integrated into an effectiveness-implementation hybrid design. If appropriate given overall study goals, hybrid designs expedite translation of research findings into routine practice [19, 21].

Apart from the benefits of understanding drug development terminology and its alignment with the study designs and methods of NIH Stage Model stages, we offer two recommendations for those who develop behavioral interventions. The first is to develop a long-term research plan that begins with the end in mind by outlining the path between an idea for an innovative behavioral intervention to large efficacy and effectiveness trials. Engaging key stakeholders (e.g., patients, clinicians, healthcare system administrators) early in the development process can ensure the intervention protocol is optimally designed for eventual dissemination and implementation in the healthcare system. The second action item is that each step in the research plan should provide sufficient information to proceed to the next step. This plan should be included in funding proposals to justify the relatively small, yet critical, steps around developing and initially testing a behavioral intervention (i.e., *Stage 0* and *I*; [50]). Researchers must convince reviewers that the long-term research plan is promising, and the current study is a natural next step in this plan.

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Declarations

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