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The Effectiveness and Cost-Effectiveness of Digital Therapeutics for Prevention and Management of Hypertension

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Abstract. Hypertension, prevalent in low- and middle-income countries (LMICs), poses a growing global health challenge. Behavioral risk modification is crucial but challenging in managing hypertension. Digital therapeutics (DTx), which are evidence-based digital interventions aimed at influencing patient behavior, offer a promising solution. This study reviews the effectiveness and cost-effectiveness of DTx for hypertension management and prevention and explores potential impacts on digital health inequalities. A systematic review of studies from three databases was conducted, focusing on DTx's role in hypertension and related risk factors. Findings indicate DTx's effectiveness and cost-effectiveness in high-income settings, though further research is needed for LMICs to address global health disparities.

Keywords: hypertension, digital therapeutics, cost-effectiveness, interventions

1. Introduction

Hypertension is a cardiovascular disease that is rising in global prevalence and is most prevalent amongst low-and middle-income countries (LMIC). Behavioral risk factor modification is a major component of preventing and treating hypertension, but also the most difficult aspect of treatment to achieve. Digital innovation has recently introduced digital therapeutics (DTx), which are clinical evidence-based therapeutic interventions using digital platforms to prevent, manage, or treat medical conditions by targeting patient behavior [1]. This study aims to review the effectiveness and cost effectiveness of DTx for prevention and management of hypertension and discuss how DTx may contribute to digital health inequalities amongst the global hypertensive population.

2. Manuscript Preparation

A systematic review with a predefined search strategy was conducted to synthesize evidence on effectiveness and cost-effectiveness of DTx interventions for prevention and management of hypertension. Three databases were searched, and search results were refined based on inclusion criteria. Effectiveness and cost-effectiveness studies were quality appraised using Drummond's Checklist and the Consort 2010 checklist. Data were extracted and analyzed using a narrative synthesis approach. Effectiveness and cost-effectiveness were either evaluated in addition to treatment as usual or alone when compared to treatment as usual. Twenty-two studies evaluated the effectiveness of DTx for hypertension and indirect risk factors of hypertension including sleep management, alcohol consumption, stress management and smoking. Three studies evaluated the cost-effectiveness of DTx for directly and indirectly treating hypertension from various economic evaluation perspectives.

2.1. Page Setup

In summary, a diagnosis convolutional network based on multi-scale convolution kernels and dropout for bearing fault type classification under variable loads is proposed in this paper. The remainder of this paper is organized as follows. Section 2 briefly introduces the search method of CNN and the theories of dropout. Then section 3 introduces the search result and the effectiveness and cost-effectiveness of the interventions. After this, section 4 gives discussions in terms of effectiveness, cost-effectiveness, health inequalities and implications on policy in detail. Final, conclusions are drawn in section 5.

2.2. Methods

A comprehensive search using a predefined search strategy was done on peer-reviewed papers in Web of Science and Scopus databases. A modified search strategy was used to identify peer- reviewed papers within Google Scholar, to which retrieved search results were restricted to the first 100 studies. A hand search of all references was done amongst the final in-scope studies to identify any additional studies to include within the systematic review. The search terms included in this study can be referenced in table 1.

This study reviewed and synthesized effectiveness and cost-effectiveness evidence on DTx that directly and indirectly treat hypertension and risk factors of hypertension that can be managed and prevented by behavioral changes. Behavioral hypertension risk factors included in the search strategy were stress, sleep management, alcohol use and smoking. We put detailed criteria in the appendix.

The search results were exported from databases into EndNote X9, where program automation features were used to remove duplicates across the three databases. Acknowledging various data field inconsistencies across the different databases, a manual search of title, abstract and author(s) was done to remove additional duplicates. Upon removal of all duplicates, results were manually screened by title and abstract to identify a pool of studies for full-text screening. In- scope full-text studies were hand-searched for any missing studies that fit the inclusion criteria.

3. Results

Upon removal of duplicates, the search strategy yielded 460 eligible studies for review. In reference to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [2], an initial screen of all titles, abstracts and keywords were done to which 352 studies (76.5%) were eliminated. Inclusion criteria in section 2.2 were used to conduct a full-text review of the remaining 99 studies (21.52%), identifying 25 studies (5.4%) to include within this systematic review.

Twenty-two of the included studies used clinical data from RCTs to assess effectiveness of DTx for management and prevention of hypertension. All were conducted in HIC, single-country settings. Most of the RCTs were conducted in the home country or region of where the DTx was developed in, without any mention of plans to expand research into other regions or country settings. The majority of the studies were set in the Americas region (n = 9, 41%), followed by the European region (n = 7, 32%), and the Western Pacific region (n = 6, 27%). Only three studies assessed cost-effectiveness of DTx for hypertension. Again, all were conducted in HIC, single-country settings, of which two (67%) were evaluated in the Americas region, and one (33%) in the Western Pacific region. There were no effectiveness or cost-effectiveness studies evaluated in LMIC settings. All the studies included within this review referenced clinical data from RCTs that were conducted amongst an adult population of ages 18+ who met the study's inclusion criteria. Most participant pools were recruited from online advertisements with a few studies recruiting from clinic settings. The majority of RCTs were conducted on populations that had access to internet and had sufficient digital knowledge. All interventions were administered remotely (i.e., at home, online) with evaluations done in clinic or remote settings. Very few studies (n = 6) focused on secondary analysis and subgroup analyses of populations such as students [3], low-income adults [4], black adults [5], adults in rural populations [6], Native Americans [7], and pregnant women [8]. Most of the RCTs excluded participants who had comorbidities, specific neurological psychiatric conditions, or were undergoing pharmacologic treatment.

3.1. Effectiveness of DTx interventions

Each of the interventions targeted behavioral modifiable risk factor change amongst study participants such as abstinence from alcohol or smoking and cognitive behavioral training for insomnia and stress management. Amongst the studies that assessed effectiveness of DTx for hypertension (n = 22), three assessed the effectiveness of DTx for overall hypertension, two for alcohol consumption management, seven for sleep management, eight for smoking cessation and two for stress management.

3.1.1. Hypertension

Three of the included studies assessed the effectiveness of DTx for hypertension in addition to TAU when compared to just TAU. Overall, DTx were found to be effective in achieving blood pressure control. The studies evaluated the primary outcome based on change to 24-h SBP levels from baseline (n =2) or adherence to medication (n =1). Two studies assessed the effectiveness of DTx HERB-DH1 for treatment of overall hypertension [9][10], a single-application DTx that targets behavioral change in reduction of salt intake, body weight control, exercise, sleep conditions, stress management, cessation of smoking and drinking alcohol [9]. Overall, findings suggested that DTx for treatment of hypertension was effective in lowering 24-h SBP levels when compared to standard lifestyle modifications [9]. Sub-group analyses suggested that DTx for treatment of hypertension may be most effective amongst drug-naïve individuals, or individuals who have no previous exposure to pharmacological treatment for hypertension [10]. In addition, DTx were found to be effective in improving adherence to secondary prevention medication for lowering SBP levels, finding that the DTx were effective in significantly increasing adherence to guideline medications and achieving controlled blood

pressure [11]. Generalizability of each of the study's findings was not recommended due to the studies' limitations around sample size and inclusion criteria.

3.1.2. Alcohol Consumption Management

Two of the included studies assessed the effectiveness of DTx for alcohol consumption management compared with TAU alone [12][13]. Both studies found that DTx for alcohol consumption management were significantly effective in improving adherence to behavioral change or lowering consumption levels of alcohol. Specifically, findings suggested that DTx were effective in achieving alcohol abstinence when compared to TAU [12, 13] as well as lowering overall alcohol consumption levels in adults [13]. Evidence suggests that DTx have a greater effect on lowering 30-day and 7-day alcohol consumption levels at 6 months when compared to 3 months [13], with both studies' findings supporting the potential long-term effect of DTx on alcohol consumption control. Findings were suggested to be generalizable to other at-risk populations for alcohol abuse [13].

3.1.3. Stress Management

Two of the included studies assessed the effectiveness of DTx for stress management, finding that DTx were effective in reducing stress and anxiety levels when compared to the results of a control group of waitlisted participants. One study was conducted amongst university students [3]and another amongst a general adult population [14]. Primary outcomes were measured by changes in Perceived Stress Scale (PSS) or State-Trait Anxiety Inventory (STAI-S-6). Findings suggested that DTx significantly reduced stress levels [14] and stress and anxiety levels together [3]. It is unclear whether effects of DTx for stress management persists after intervention, as both studies mentioned reservations on the effect duration over time. Both studies indicated that quality of the data prohibited generalizability of findings to other populations.

3.1.4. Sleep Management

Seven of the included studies assessed the effectiveness of DTx for sleep management compared with TAU alone. The control group's assigned TAU intervention varied from standard sleep hygiene education and/or pharmacologic treatment (n = 4), other digital sleep interventions (n = 2) or no treatment (n =1). Primary outcomes for effectiveness of DTx for sleep management was measured by indicators such as change in Insomnia Severity Index (ISI) (n = 2) [8, 15], sleep onset latency (SOL) (n = 1) [16], Sleep Condition Indicator score (SCI-8) (n = 2) [17][18], Sleep Efficiency (SE) (n = 1) [19]and Glasgow Sleep Impact Index (n = 1) [20]. Each of the studies found that DTx when compared to TAU were significantly effective in improving sleep patterns and overall health amongst the study population. In addition to improvements in sleep patterns, studies have found that DTx for sleep management may also be effective in reducing depressive symptoms [18] and improving workplace productivity [20] Two studies suggested the generalizability of its findings to other populations with similar characteristics [18, 20].

A summary of effectiveness study characteristics, design and outcomes can be referenced in table 2.

3.2. Cost-effectiveness of Interventions

Amongst the included studies, each took on a different single-country economic evaluation perspective, including a public payer perspective [21], US payer perspective [22] and a societal perspective [23]. Two studies assessed the cost-effectiveness of DTx for hypertension, finding that while DTx increase the cost of hypertension treatment when compared to TAU [21, 22], it remained cost-effective. Nomura et al., (2022) found that monthly costs of DTx had the greatest effect on cost-effectiveness, which should be considered when replicating findings in different country settings. In addition, DTx were associated with significant health resource utilization (HRU) savings, finding HRU most sensitive to pharmacologic TAU and clinical inertia during year 1 [22]. Limitations on these studies involved lack of generalizable findings, potential diminishing treatment effects and utilization of estimates of clinical effectiveness data.

Of the three studies that assessed the cost-effectiveness of DTx for prevention of hypertension, two studies assessed the cost-effectiveness of DTx for overall hypertension and one assessed the cost-effectiveness of DTx for treating insomnia [23]. Two studies referenced clinical effectiveness data from RCTs [22, 23]and one study referenced published estimates of clinical effectiveness data within a decision analytic model framework [22]. Overall, each of the studies found DTx to be very cost-effective when compared to no treatment or TAU alone.

A summary of cost-effectiveness study characteristics, design and outcomes can be referenced in table 3.

4. Discussion

There are few notable limitations for this systematic review. Considering the new and inconsistent usage of the term "digital therapeutics (DTx)", various researchers have likely conducted effectiveness and cost-effectiveness analyses on DTx and classified the interventions under other frequently used terms (e.g., digital health, mobile health). Therefore, it is likely that several relevant

studies were missed and excluded from this review. Secondly, this review considered only full economic evaluations rather than partial economic evaluations such as cost analyses, which may also be helpful for decision makers in allocating resources. Thirdly, the studies included in this review evaluated single interventions, making it unclear whether multiple DTx are effective for treatment of multiple risk factors for hypertension. Thus, future studies should evaluate the effectiveness of two or more DTx for treatment of two or more conditions.

At the country level, cost-effectiveness evidence can aid in decision making for private and public providers of insurance around which services to cover and how much should be allocated towards reimbursement. More economic evaluation evidence around cost- effectiveness of DTx can aid decision makers in allocating resources towards covering a wider range of DTx, ultimately helping to improve accessibility and rates of adoption across populations and various health conditions. Therefore, cost-effectiveness evidence conducted within LMICs and within-country settings is essential for policy makers to understand where to allocate and reallocate resources sustainably to improve health outcomes amongst the hypertensive populations.

This review has found that when compared to standard TAU alone, DTx are more effective in treating overall hypertension and modifiable indirect risk factors for hypertension. Considering the challenge around achieving lifestyle behavior changes, these findings suggest that DTx that target behavioral change may be more effective within certain at-risk hypertensive populations when compared to standard TAU. Amongst the twenty-two effectiveness studies included in this review, only three assessed the effectiveness of DTx for management and prevention of overall hypertension, with two evaluating a common DTx brand, HERB-DH1. The most amount of evidence was available for sleep management and smoking cessation risk factors. Amongst other risk factors and overall hypertension, the amount of effectiveness evidence appears equally spread. Additional research may be needed for stress management and alcohol consumption risk factors. Research has shown that increased stress levels contribute to short and long-term high-blood pressure, which may lead to other conditions such as anxiety and depression [24]. High levels of alcohol consumption may cause hepatic, gastrointestinal, nervous system, and cardiovascular conditions, leading to overall poor health outcomes [25]. Effect size and direction within and across the risk factors could not be compared due to present heterogeneity in primary and secondary outcomes, study setting and intervention type [26]. Thus, a meta- analysis or subgroup analysis for each risk factor could not be done during this review. While it is not possible to compare outcomes between studies in this review, overall direction of the effect remained consistent across the three studies on overall hypertension; however, significance and effect size varied based upon sample size. Amongst the four included indirect risk factors for hypertension, this review found a variation in how primary outcomes were measured within risk factors. For risk factors such as stress and alcohol consumption, additional outcomes were often measured on improved mental health conditions, which was not considered within the scope of this review. While it is also not possible to compare outcomes between studies, the significance and direction of the effect were consistent within risk factor groups. Thus, a meta-analysis may be able to be conducted with future additional research.

5. Conclusion

As the world transitions to a more digitized environment, technology is one of the many driving forces of healthcare innovation and improved health outcomes. Digital health innovation offers the potential to advance health outcomes by lowering cost to care, increasing accessibility to quality care and personalizing care delivery [27]. These improvements may contribute to the empowerment of individuals in taking ownership of their health outcomes [28], which can benefit the patient-provider relationship and improve the efficiency of health systems [29]. This review found that DTx for direct and indirect management and prevention of hypertension appears to be an effective intervention in HICs for targeting behavior change in modifiable risk factors for hypertension; however, there remains a large gap in research conducted on LMIC and high-risk subgroup populations. As risk factors and social factors shift and evolve, continuous research becomes even more important. Addressing these gaps in the coming years will aid providers and decision makers in understanding how to prescribe quality treatment and sustainably allocate resources to address the growing global burden of hypertension. Until then, DTx has the potential both improve and worsen health outcomes amongst the global hypertensive population. Which effect is stronger? —We are yet to know.

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