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Can mindfulness training improve medication adherence? Integrative review of the current evidence and proposed conceptual model

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Abstract

Medication adherence is a complex, multi-determined behavior that is often influenced by system- (e.g., cost), drug- (e.g., regimen complexity), and patient-related (e.g., depression) factors. System-level approaches (e.g., making medications more affordable) are critically important but do not address patient-level factors that can undermine adherence. In this paper, we identify patient-level determinants of non-adherence and discuss whether mindfulness-training approaches that target these determinants can help to improve adherence to medical treatment. We highlight two chronic medical conditions (viz., heart failure, HIV) where poor adherence is a significant concern, and examine the evidence regarding the use of mindfulness interventions to improve medication adherence in these two conditions. We also discuss the theoretical underpinnings of mindfulness training with respect to medication adherence, and conclude by suggesting directions for future research.

Introduction

Adherence has been defined as “the extent to which a person’s behavior (e.g., taking a medication, following physical activity prescriptions, attending clinics) coincides with medical advice.” (1) Adherence is a multi-determined behavior, influenced by socioeconomic, health care system-, treatment- and patient-related factors. (2) Patient-level factors (e.g., depression, poor cognitive function, substance use) play an important role in determining adherence and interact with system-levels factors in ways that are often unpredictable and unique to each patient. (2)

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Poor adherence to medical regimens is a significant clinical and public health problem. Regardless of the disease or the population considered, poor medication adherence is highly prevalent, even in survivors of serious diseases. Among patients recovering from an acute myocardial infarction, 8% to 20% are no longer taking key medications (such as ACE inhibitors, statin, and aspirin) 6 months after hospital discharge.(3) Among patients with heart failure (HF), medication adherence rates average only 50% (4) and declines over time even among patients who are initially adherent. (5–7) Only about 30% of HIV-positive individuals adhere to antiretroviral medications to the point of achieving viral suppression. (8, 9)

Adherence behaviors have been targeted by a range of interventions. A review by the Agency for Health Care Research and Quality found that the most effective approaches are policy-level interventions, such as programs to lower cost by reducing out-of-pocket expenses, case management, and educational interventions. Some patients, however, remain poorly adherent even when such policy-level interventions are implemented, indicating that system-level approaches are necessary, but likely not sufficient in all patients. More comprehensive adherence approaches that address patient-level determinants of medication adherence are needed.

In this paper, we discuss the possible usefulness of mindfulness training to improve medication adherence, focusing on two chronic conditions: heart failure (HF) and HIV. We chose these conditions as examples because (a) both are chronic diseases in which poor medication adherence is prevalent, and (b) in both conditions, poor medication adherence has major consequences on clinical outcomes. First, we identify patient-level barriers to adherence. Next, we describe mindfulness interventions, review the evidence in support of mindfulness training to improve medication adherence, and present a conceptual model illustrating the possible mechanisms by which mindfulness training might improve adherence. We conclude by making recommendations for future research.

Example 1: Heart Failure and Poor Medication Adherence

Heart failure (HF) is characterized by the inability of the heart to pump the necessary amount of blood to the peripheral tissues. Symptoms include shortness of breath, fatigue, limited exercise tolerance, and fluid retention. (10) Due to the aging of the population, HF is becoming increasingly prevalent in Western countries; (11) in the United States alone, 5.7 million individuals are currently affected. (12–16) The prognosis of HF is largely unfavorable, with hospital re-admission rates reaching 50% within 6 months of discharge (17, 18) and 5-year mortality rates of 50%. (10, 14, 19) Medical therapy improves symptoms and reduces re-hospitalizations and mortality, (20, 21), however such treatments are effective only if patients take their medications regularly; instead, adherence to pharmacological treatment among HF patients is, on average, only 50% (4) and tends to decline over time even among individuals who were initially adherent.(5–7) Poor medication adherence results in high rates of emergency room visits, hospital re-admissions, and mortality. (22–27)

Patient-level Barriers to Medication Adherence in Heart Failure

At the patient level, cognitive impairment, sleep disorders, and depressive symptoms have all been associated with poor adherence.

Cognitive impairment is prevalent among HF patients: in a study conducted among veteran outpatients, previously unrecognized cognitive impairment was found in 58% of subjects; verbal learning, immediate memory, and delayed verbal memory were most impaired. (28) Another study found that a similar proportion of adults with HF had below average measures of cognitive function. (29) Measures of cognitive impairment such as forgetfulness, (4) attention lapses, (30–32) and poor executive function (33) have all been associated with poor medication adherence among adults with HF. The lapses in attention reported among HF patients reduce the patients' ability to develop consistent adherence patterns; in fact, attentional lapses have been significantly associated with poor medication adherence, (30–32) and forgetfulness is one of the most common barriers to adherence in this population. (4)

Sleep disorders are common among HF patients. (34, 35) Excessive daytime sleepiness (EDS; a consequence of poor sleep quality), (35) was a significant predictor of poor medication adherence in a longitudinal study conducted among 280 HF patients, with 10% increases in non-adherence per each unit increase in EDS ($p = .008$). (30) Another longitudinal study found that daytime sleepiness was associated with a steep decline in objectively measured adherence. (31) One mechanism by which excessive daytime sleepiness may result in poor adherence behaviors is through cognitive impairment and impairment in vigilant attention. (36) Indeed, EDS has been associated with below average performance on the digit symbol substitution task, a sensitive measure of cognitive performance in HF patients. (29)

Finally, depressive symptoms are reported by about 60% of HF patients (both hospitalized patients and outpatients) (37) and have been associated with poor adherence to medical treatment. (4, 38)

Example 2: HIV/AIDS and Poor Medication Adherence

More than one million adults and adolescents in the United States are currently living with HIV, a virus that attacks the body's immune system and specifically CD4 cells. (39) If left untreated, HIV progressively reduces the number of CD4 cells and makes the individual susceptible to opportunistic infections and to infection-related cancers. Although there is no cure for HIV, this disease can be controlled successfully with medical treatment. Antiretroviral therapy (ART) has changed the course of this disease by improving viral suppression, reducing infectiousness and HIV-related morbidities, and increasing survival. (40–42) Strict adherence to ART is recommended (43) and yet only 30% of persons living with HIV (PLWH) adhere to ART to the point of achieving viral suppression. (8, 9) Sub-optimal adherence to ART compromises individual health, increases health care costs, and can lead to the development of ART-resistant strains of HIV. (42, 44)

Patient-level Barriers to ART Adherence among PLWH

Among the patient-level barriers to ART adherence among PLWH, life stress and depression are particularly important. (45)

Life stress is common in PLWH. The HIV epidemic disproportionately affects people with considerable economic disadvantage, including those who live in poverty, are homeless, and who experience food insecurity. (46) In addition, many PLWH are members of socially discriminated groups, including racial/ethnic minorities, sexual minorities, and people struggling with mental health or substance use problems. (47–50) HIV remains a stigmatized disease, and some PLWH are reluctant to disclose their serostatus for fear of social rejection. Life stress is important for disease progression because, in addition to undermining ART adherence, stress can directly suppresses immune functioning (and levels of CD4 cells), thereby exacerbating the effects of poor adherence on viral load.

Depression is also a frequent problem given the life-threatening nature of HIV combined with the stressful life circumstances described above. (51, 52) Both depression and stress have been strongly associated with poor ART adherence. (45, 53–62)

Interestingly, predictors of non-adherence to medications among patients living with HF and HIV are similar. Both conditions are associated with depression, which often undermines sleep, which is in turn necessary for optimal cognitive functioning. Indeed, all three factors have been associated with non-adherence across many chronic diseases. Specifically, a meta-analysis of 31 studies involving 18,245 participants found that depressed patients were 1.76 times more likely to be non-adherent than non-depressed patient, and the association was consistent across different chronic conditions. (63)

Mindfulness Training and Medication Adherence

Mindfulness is the most common translation of the word “sati” in Pali, the language in which the most ancient Buddhist texts were originally written. A different translation, perhaps better rendering the fact that mindfulness can be cultivated through practice, (64, 65) is “to be mindful.” Mindfulness has been defined as a “the act of paying attention in a special way – in present moment, with kindness, and non-judgmentally.” (66) Although Western psychology places great emphasis on these “attentional” and more “static” qualities of mindfulness – and certainly such aspects receive great attention in the early phases of mindfulness training – Buddhist scholars have highlighted the cognitive aspect of mindfulness and its connections with working memory. Another meaning of “sati” is in fact “to remember, to keep in mind.” (67)

Mindfulness training (MT) programs – including the well-known Mindfulness-Based Stress Reduction program (MBSR) (66) – are adaptations to a Western, secular context of meditation practices rooted in the Buddhist tradition of the South Eastern regions of Asia. (66) In general, mindfulness training involves learning to notice events arising in the field of consciousness at any given moment and to re-direct attention to the breath (or to any other chosen focus of attention). Research has shown that the cultivation of this particular way of focusing and redirecting attention facilitates self-regulation and strengthens the ability of the

individual to avoid absorption in maladaptive and habitual mental patterns, behaviors, and emotional reactions. (68–70)

There is mounting evidence supporting the efficacy of MT on several of the aforementioned patient-level barriers to adherence. Consequently, the potential therapeutic value of mindfulness training for medication adherence has been the subject of research interest in the past decade. We hereby present a summary of the evidence supporting the efficacy on MT on several determinants of adherence behaviors in HIV and HF patients, namely, stress, depressive symptoms, cognitive impairment, and sleep.

Stress and depressive symptoms

A meta-analytical review of 39 studies of MT for a range of psychiatric or medical conditions reported that MT led to robust and sustained reductions in self-reported anxiety and depressive symptoms (Hedge s $g = 0.95$). (71) A systematic review of 31 RCTs found medium-sized post-intervention effects for depression ($g = 0.54$) and for stress/distress ($g = 0.56$). (72) Another meta-analysis of studies focusing on participants with a current depressive or anxiety episode found significant benefits on depressive symptom severity for MT relative to controls (73). Three recent meta-analyses reported significant effects (and moderate effect sizes) of MT on depressive symptoms among patients with diverse medical conditions, (74–76) and a meta-analysis of MT delivered online had a significant beneficial impact on depression, mindfulness skills, and stress, with effect sizes ranging from small to moderate. (77)

Cognitive function

The role of attention in cognitive processing consists in selecting which sensory input, among many present at any given moment, will be processed for memory storage and/or further processing. Attention works in two “operating modes” (a) it can be involuntarily captured by salient stimuli from the environment (“alerting attention”) (78) and (b) it can be voluntarily directed according to the needs or purposes of the individual (“oriented attention” (79, 80). Alerting attention is critical for situations that require a rapid response (e.g., an environmental threat). However, in modern life, the threats we face are less immediately existential. Therefore, to complete most tasks, we must ignore irrelevant stimuli and focus instead on stimuli that are relevant for our goals. Neurophysiological studies have shown that the ability to override irrelevant stimuli is associated with working memory capacity, thus indicating that the ability to sustain attention is fundamental for cognitive processing. (81) The initial phases of MT, which emphasize concentration practices (i.e., focusing the attention on the sensations associated with breathing and on bodily sensations), have been shown to improve selective and executive attention. (82–84) Both observational and experimental studies have shown that MT improves memory and cognitive performance. (84) For example, a RCT of a 2-week mindfulness intervention conducted among graduate students demonstrated that mindfulness training improved working memory capacity and reduced the occurrence of distracting thoughts during completion of the graduate record examination. (85) Jha et al. observed an increase in working memory capacity among military personnel who underwent an 8-week mindfulness intervention compared to both military and civilian control groups. (86) A study conducted among experienced meditators

showed better performances on all attention measures compared to controls without meditation experience. In the latter study, the duration of individual mindfulness practice correlated positively with measures of attention. (87) Finally, a RCT conducted among 201 older adults demonstrated that participants trained in MBSR showed significant improvements in measures of executive function compared to those in the wait-list control group. (88)

Sleep

Numerous experimental and observational studies across diverse patient populations have found that mindfulness interventions improve sleep quality. (89–93) Significant improvements in sleep quality were found in a RCT of MBSR for women with post-menopausal symptoms versus a wait-list control group. (90) Our group detected improvements in sleep quality ratings after MBSR training compared to baseline among healthy individuals. (89) Gross et al. found that mindfulness training was as effective as pharmacological treatment in improving objective and subjective measures of sleep among adults with chronic insomnia. (92) Another RCT demonstrated that an 8-week mindfulness-based intervention conducted among depressed individuals improved objective (polysomnographic) and subjective measures of sleep, decreased wake time, and increased sleep efficiency. (93)

Evidence supporting the effect of MT on medication adherence. Despite the large body of literature supporting the efficacy of MT on key patient-level determinants of adherence, few studies have investigated the effect of mindfulness training on medication adherence. In the context of cardiovascular disease, there have been no studies of the effect of MT on adherence even though the possible benefit has been suggested. (94) In the context of HIV/AIDS, there has been only very limited research. A RCT explored the efficacy of MBSR compared to a wait-list control group on symptoms and bother/distress related to ART side effects (primary outcome) and self-reported medication adherence (secondary outcome). Results did not show any improvement in ART adherence. (95) It is important to note, however, that in this study, baseline ART adherence was already high, thus undermining the chance to observe improvements (i.e., a ceiling effect). Results from a pilot RCT of MBSR for stress reduction in HIV-infected youth have shown that the intervention group was more likely to have a lower viral load at follow-up ($p = .04$) compared to the control group, a finding that could be explained by improved ART adherence. (96) A large RCT to determine efficacy of MT on ART adherence among HIV-infected urban youth is now under way (ClinicalTrials.gov NCT02624193).

Proposed Conceptual Model Linking Mindfulness Training and Medication Adherence

The benefits of mindfulness training hinge upon two assumptions. First, we assume that patients receive an adequate dose of the MT intervention both with respect to instruction and individual practice. (97) Second, we assume that mindfulness is a skill that can be cultivated through training and practice. Despite the limitations and challenges encountered in the measurement of mindfulness, (98) studies have shown that mindfulness skills improve in

response to training and that the effect of mindfulness interventions on various health outcomes is mediated by improvements in mindfulness levels. (64, 65, 97)

Our model builds upon two extant theories of mindfulness, (68, 69) and on empirical evidence regarding the efficacy of MT on predictors of medication adherence (viz., cognitive impairment, poor sleep quality, depressive symptoms, and stress). Guided by theory and research, we propose the following conceptual model to guide future research. As shown in Figure 1, we posit that mindfulness training could improve adherence via improvements in attention and working memory, sleep, stress and depressive symptoms. Positive changes in adherence will in turn result in improvements in biomarkers and clinical outcomes.

We note that the proposed model is a only a “roadmap” to guide future research on mindfulness and medication adherence and it is by no means exhaustive of all the possible ways in which mindfulness training can affect the various factors that influence medication adherence. This model will likely evolve as new experimental evidence confirms or refutes our hypotheses, and as research shows that mindfulness training can affect other important patient-level determinants of medication adherence.

Directions For Future Research

As noted above, currently available interventions to promote medication adherence do not sufficiently target important patient-level determinants of adherence. Mindfulness interventions have been proven effective on several predictors of poor adherence (i.e., sleep, cognitive impairment, depression, and stress) and thus hold great potential to improve medication adherence. At present, however, there is only limited, preliminary evidence for an effect of mindfulness training on medication adherence. Future studies should be well-designed randomized controlled trials including both self-reported and objective measures of adherence (e.g., MEMS caps or pill counts), rigorous intervention protocols, and monitoring of intervention fidelity. In addition to traditional class-based training, non-traditional mobile-health approaches (i.e., web-based training, phone delivery, and smartphone mindfulness applications) hold great promise for removing barriers to access (e.g., transportation, parking, group scheduling), reducing costs, and for promoting the dissemination of mindfulness interventions. (77)

In sum, based on the previously expounded arguments, we believe that the exploration of the role of mindfulness meditation in the promotion of medication adherence is a worthwhile research endeavor that has great potential to contribute to the improvement of this relevant public health problem.

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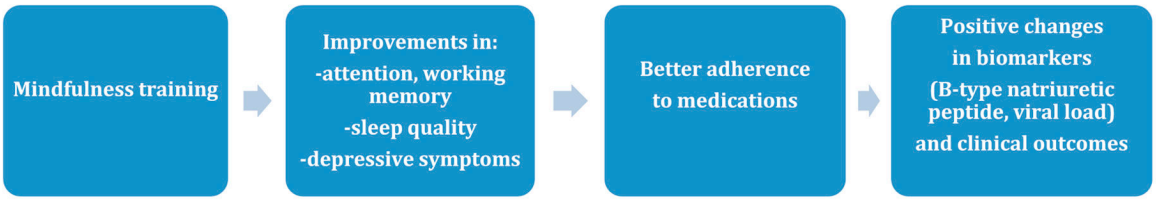

Figure 1.