Fullscript

Treatment adherence in integrative medicine

Comprehensive literature review and industry insights: a brief report

Note: The information provided in this report is based on a review of literature available at the time of publication. While the content is considered to be accurate at the time of publication, new or updated research released after the publication date may impact the accuracy of the information. Please use your discretion when using this resource.

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Preface

As part of its mission to change how health is prescribed, Fullscript developed this report to contribute to the growing knowledge of treatment adherence in integrative medicine. The insights contained in this report may inform the development of adherence-based educational opportunities and content in functional and integrative medicine, as well as future adherence-related features within the Fullscript platform.

About Fullscript

Fullscript is an industry-leading health technology platform that facilitates virtual dispensing for practitioner-grade supplements and develops evidence-based clinical research and educational content to contribute to the rapidly emerging field of integrative medicine. In order to meet the needs of its practitioners, support their treatment recommendations for patients, and advance scientific understanding in the area of treatment adherence, Fullscript sought to combine a comprehensive literature review strategy with practitioner interviews, surveys, and internal data, as outlined in this report.

Conflicts of interest

The authors of this report are employed by Fullscript as part of the Integrative Medical Advisory (IMAT) and Insights teams. They received no additional compensation for the production of this report and are not affiliated with any particular brands, products, or institutions. The authors aimed to provide an unbiased review of the literature in this area with the ultimate goal of providing practitioners with the knowledge and tools to help improve treatment adherence and subsequent outcomes for their patients. Our hope is that this report supports the continued development of research in the area of treatment adherence, particularly as it pertains to integrative medicine.

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Executive summary

Purpose

Treatment adherence is a topic that is well studied but not well understood. Low treatment adherence is a significant issue that limits the effective management and treatment of chronic conditions, creating significant healthcare burden, costs, and poor patient outcomes. Still, there **is no broad or straightforward solution to address non-adherence to treatment.**

$100–290 billion

Estimated cost of non-adherence to the U.S. healthcare system [15, 87]

30–69%

Estimated rate of hospital admissions due to medication non-adherence [86, 97]

The **complexities and interplay between factors that may influence treatment adherence necessitate a personalized approach** to understanding, identifying, analyzing, addressing, monitoring, and evaluating both the reasons for non-adherence and the strategies that may facilitate acceptance of and commitment to treatment plans. [60, 67, 77, 142, 162, 177]

The Centers for Disease Control and Prevention (CDC) estimates that: [20]

60%

of U.S. adults live with at least one chronic disease

40%

of U.S. adults live with two or more chronic diseases

This report provides a review of the factors that influence treatment adherence, describes current limitations for how adherence is measured, and provides insight into some of the most well-studied interventions that may improve treatment adherence, particularly in the context of medication use. The report also includes findings from a set of studies conducted by Fullscript, drawing upon insights collected from integrative practitioners using the Fullscript platform to recommend supplement and lifestyle-oriented treatment plans.

Key findings

Our literature review illustrated the complexities within treatment adherence research and management. There are many ways to measure and interpret treatment adherence depending on practitioner, patient, and intervention-related considerations. Generally, treatment adherence rates decline for all patients over time, and the likelihood of this is influenced by several hundred different factors, such as practitioner/patient education, cost, feasibility, and patient readiness to change. Proposed interventions should consider underlying barriers to adherence and treatment-related factors, and may vary depending on the stage of disease management.

Our Fullscript practitioner survey and interviews identified similar themes. Practitioners listed factors such as cost and patient's feelings of being overwhelmed and readiness to change as primary barriers to adherence. To increase the likelihood of adherence, all practitioners should consider establishing trust with patients, using a slow and simple treatment approach (so as not to overwhelm patients), scheduling regular follow-up appointments, having clear and open communication, and using an evidence-based approach to rationalize treatment choices and monitor progress.

Practical strategies for improving adherence

1. Realistic cost

- Consider whether options with health insurance coverage are available.
- Use a staged approach to introduce treatments one at a time and set realistic goals in line with financial restrictions.

2. Patient readiness

- Assess the likelihood a patient will adopt a behavior by asking open-ended questions about motivations, attitudes, and beliefs about treatment.
- Practice strategies such as motivational interviewing or other theoretical and evidence-based behavior strategies to communicate empathy and a shared partnership/investment in the patient's well-being.
- Provide education to reassure the patient about the availability of evidence-based treatments and how they work, potential side effects of treatment, information about the condition, and the importance of adherence.
- Use lab testing to help demonstrate the need for treatment and track progress.

3. Staged approach

- Facilitate treatments with simplified regimens via reduced dosing frequency (e.g., sustained-release) and fewer therapies (e.g., combined pills).
- Provide multiple options for increased flexibility.
- Suggest the use of pre-assembled dosing (e.g., blister packs), pill organizers, or other methods that can remind patients whether a dose was used or not.
- Link treatment with a patient's simple daily habits (e.g., teeth brushing).
- Be clear about which aspect of the health problem to prioritize.

4. Communication

- Provide multiple opportunities for treatment reminders using tools like text messages, phone calls, and applications.
- Provide feedback on adherence using quantitative and qualitative data.
- Provide multiple points of contact and follow up in between appointments to determine how the treatment is coming along.
- Provide opportunities for in-clinic and face-to-face interactions when possible.

5. Streamline care

- Involve other practitioners with various training and schedule flexibility in the process or provide referrals.
- Incorporate multiple strategies as necessary, particularly with behavioral and educational components, for long-term adherence assistance.
- Engage in adherence training as a professional development opportunity.

Part one

Review of literature on treatment adherence

Key findings

1. Treatment adherence is conceptualized and studied predominantly within the realm of conventional (pharmaceutical) therapies, but themes may transcend to other medical models.

2. Several terms related to adherence, including “compliance” and “concordance,” have been used interchangeably in the literature, but it is commonly accepted that they have slightly different connotations.

3. There are several ways to measure treatment adherence, but there is no single gold standard. Comparison of adherence rates can be difficult as studies often do not use the same measures or define adherence under the same parameters (e.g., dichotomous vs. continuous variables).

4. Several hundred factors may interactively influence the likelihood of adherence. Practitioners should identify the most relevant factors for each patient.

5. Interventions that improve medication adherence may target various facets of treatment, but adherence rates generally decline over time. New technology will provide opportunities to improve assessment and the likelihood of adherence.

How to improve treatment adherence

Practitioner education

Become familiar with the factors that influence treatment adherence.

Proactive screening

Proactively identify barriers to adherence and provide strategies prior to treatment initiation.

Continue to measure

Use multiple measures to best capture adherence rates and reasons for non-adherence.

Implement key strategies

Provide strategic interventions specific to the identified reasons for non-adherence.

Literature review methodology

The literature review used a semi-systematic, mixed methods approach to assess the current state of knowledge and synthesize themes across multiple disciplines. [151] The primary search strategy combined the search terms "adherence" or "compliance" in PubMed® with various keywords identified for this review (e.g., assessment, patient, medication, diet) and yielded over two million articles, including duplicates. The search strategy on interventions to improve medication adherence included a combination of the search terms "medication adherence[Mesh]" and "interven*".

The inclusion of systematic reviews and meta-analyses were prioritized, followed by clinical trials or other supportive articles where required. However, there were no rigid inclusion or exclusion criteria.

Search entry examples:

Treatment adherance and compliance[Mesh]

Medication adherence[Mesh] AND interven

Adherence AND measure

Adherence AND barrier

Defining adherence

Variability exists when defining and measuring "adherence" to a treatment. [142] There has been a shift from using the term "compliance" to the word "adherence" as literature and medical practice have come to recognize the importance of the therapeutic alliance. [7] However, despite subtle differences in their meaning, these terms have been used synonymously. [170]

Therapeutic alliance:

The relationship between a patient and practitioner that encourages agreement on treatment goals and tasks as well as a positive personal relationship

Compliance

Compliance is defined as the extent to which a patient's behaviors follow a practitioner's prescribed treatment plan (e.g., medication, diet, lifestyle changes, etc.). It often implies a patient's subservience to the practitioner's recommendations and infrequently considers patient treatment preference or values. [142, 170]

Adherence

Adherence is defined as the extent to which a patient's behaviors follow an agreed-upon prescription or therapeutic regimen. It considers the patient's views and choices, and it allows them to play a more active role in the development of the treatment plan. [11, 142, 170, 111]

Intentional non-adherence:

Deliberate abstinence from a therapy

Unintentional non-adherence:

Sporadic or accidental lapses in the degree to which a treatment plan is followed

Concordance

Concordance is the element of adherence that describes the state of cooperation and mutual agreement to a prescribed treatment plan between a practitioner and their patient. Concordance reflects the increasing emphasis placed on the shift from a patient's subservient acceptance of a treatment plan to the therapeutic cooperation between patient and practitioner. [170] The use of shared decision-making strategies to empower patients in disease self-management and treatment adherence has been increasingly recognized. [12, 75, 82, 145]

Frameworks of adherence and influencing factors

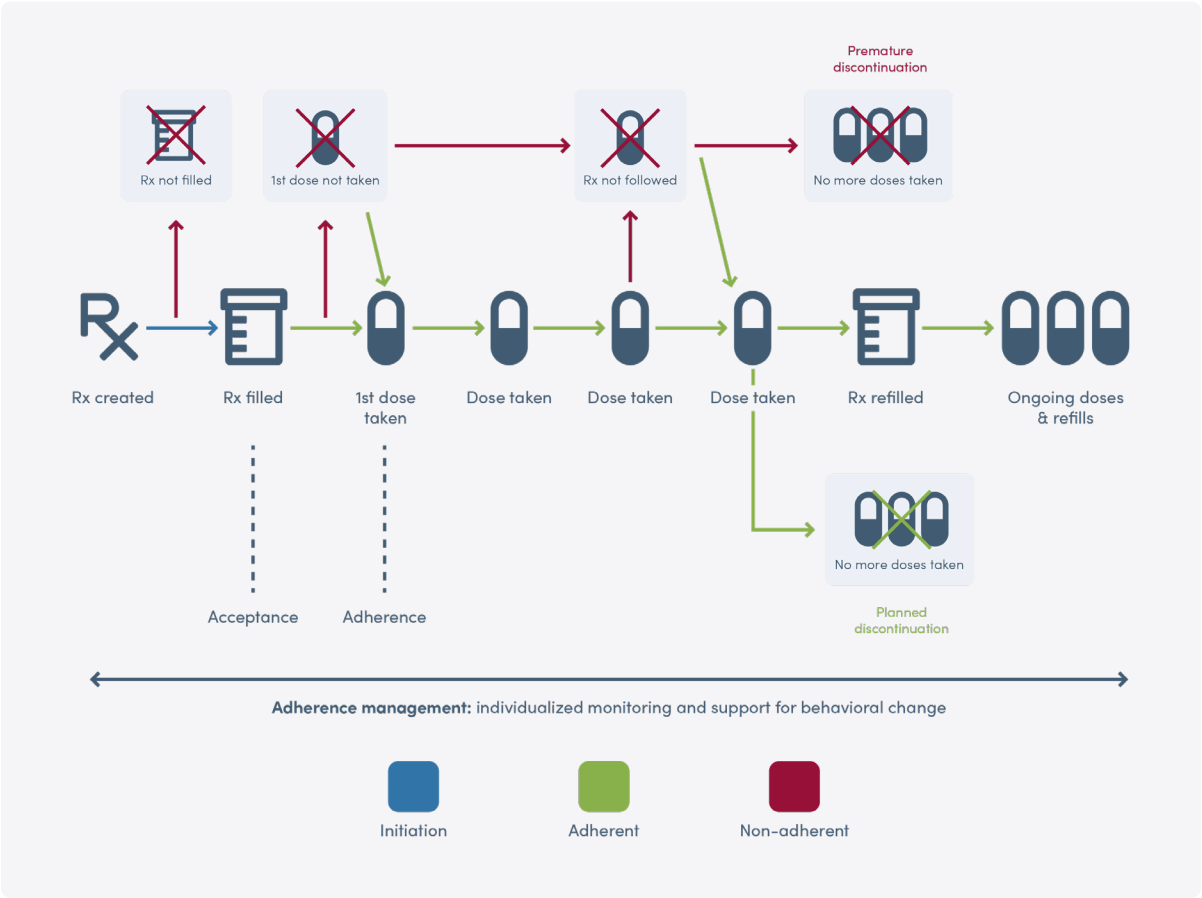
Various theoretical models of treatment adherence have been proposed. Please note that the following examples are merely used to illustrate some of the types of theoretical models available to conceptualize adherence. These examples are not meant to be a comprehensive or exhaustive list.

The process of medication adherence and its management

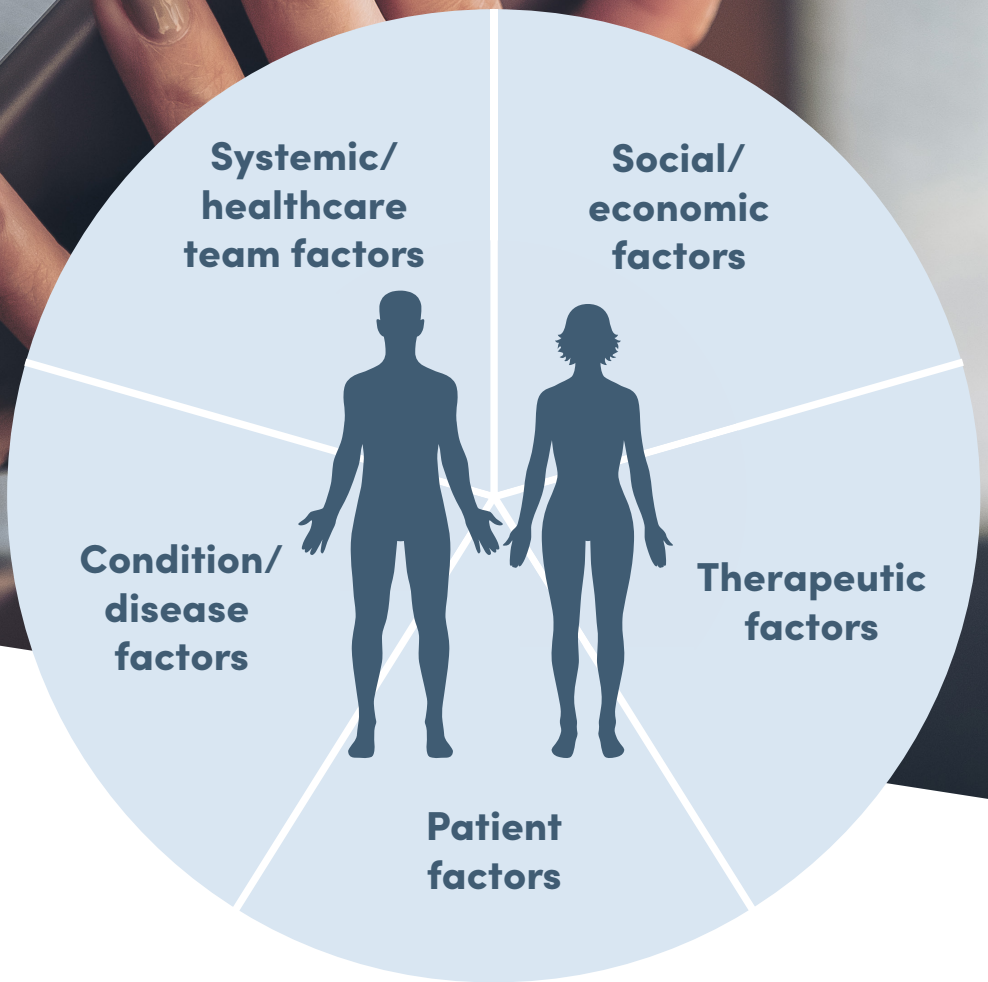
Within this framework, adherence to medications is the extent to which patients use their medication as prescribed during three phases:

1. **Initiation (primary adherence):** the point at which a patient takes the first action, step, or dose, etc., of a prescribed treatment plan [153, 170]
2. **Implementation (secondary adherence):** the degree to which a patient follows their treatment plan from initiation to discontinuation [170]
3. **Discontinuation:** the point at which the treatment plan halts regardless of the rationale or whether it was intentional or unintentional [170]

The Fullscript model of adherence management



"Adherence management" refers to the ongoing assessment and support from healthcare systems, prescribing policies, communities and organizations, practitioners, family and caregivers, and patients. [170]



The WHO's five dimensions of adherence [142]

The World Health Organization's five dimensions of adherence

The World Health Organization's (WHO) report on adherence describes five interacting dimensions that influence adherence to treatment plans within states of chronic disease. [142] Non-adherence has been traditionally considered as a patient-centered problem.

Therefore, interventions to improve adherence have primarily focused on targeting patient-related factors without critical reflection on the interplay of the other four dimensions. [86, 87, 126, 142]

The WHO's five dimensions of adherence include:

Condition/disease factors

Symptom severity

Extent of physical, psychological, social, educational, or employment disability

Development course or state of the condition

Presence of co-morbidities

Existence of treatments available

Patient factors

Forgetfulness

Negative feelings like stress, hopelessness, or anxiety towards treatment or the condition

Level of motivation, self-efficacy, or knowledge of the disease and therapy

Perception of therapeutic expectations, effects, efficacy, or need for treatment

(Mis)understanding of the disease, diagnosis, or therapeutic protocol

Social/economic factors

Age, race, and gender

Poverty or employment status

Literacy level and education

Social and family support

Living location and transportation access

Treatment cost

Culture or social beliefs of the treatment or disease

Systemic/healthcare team factors

Patient-practitioner relationship

Availability or scope of care/coverage

Access to treatment

Practitioner education, workloads, incentives, and feedback

Time constraints, follow-ups

Systemic patient education

Establishment of community support and self-management programs

Therapeutic factors

Protocol complexity

Therapy duration

(Un)success of previous treatment

Frequency of treatment adjustments

Speed of therapeutic benefits

Presence of adverse effects

Availability of medical support for side effects

It is important to note that these factors have been primarily studied within the realm of conventional medicine. However, the factors influencing adherence transcend medical dogmas, whereby significant overlap of these factors similarly influence adherence to other treatment options including diet, physical activity, or complementary and alternative medicines (CAM), including supplements. [40, 45, 46, 50, 81, 92, 96, 122, 124]

Examples of some factors that specifically relate to these alternative treatment options include:

Complementary and alternative medicines

Strong belief in holistic health

Positive attitudes or appreciation of CAM-based therapies

Belief in environmental pollution as a negative health factor

Perception that other treatments are costly [45]

Diet and nutrition

Knowledge of specific diets, instructions, nutrition labels, and adapting recipes [1, 10, 17, 62, 121, 152]

Limitations of foods/supermarkets, cost [1, 10]

Cultural connections with food, history of poor diet [1, 10, 48, 62, 152, 180]

Intensity/difficulty of the diet, food palatability [17, 68]

Physical activity and exercise

Availability of exercise facilities, equipment [64, 127, 136, 139, 141, 149]

Level of fatigue, physical limitations/injury [18, 53, 127, 136, 149]

Observed or perceived lack of time, weight loss or change in body composition [18, 136, 139, 149]

Cultural/social perspectives on appropriateness of exercise [18, 64, 141]

Lack of enjoyment of exercise or knowledge/training [18, 136]

Type of exercise, whether it is supervised, performed in groups, etc. [104, 127, 133, 136]

Supplements

High number of pills, frequency of doses [33, 40, 122]

Low frequency of clinical visits/follow-up [40]

Forgetfulness [40, 122]

Presence of fear of side effects [40, 122]

Modes of administration (e.g., capsule, tablet, liquid, injections) [122]

Supplement characteristics (e.g., size, taste, smell, color, taste fatigue) [47, 66, 122]

Measuring adherence

Adherence may either be measured as a binary/dichotomous or continuous variable. As a binary variable, the individual may either be adherent or non-adherent. As a continuous variable, adherence is measured as the degree to which the patient precisely follows the treatment plan.

For example, suppose a patient is provided with three recommendations within their treatment plan. In this case, he/she may be adherent to one aspect of their plan, may choose not to initiate or fulfill another, or may not demonstrate **persistence** with the third portion of the recommendation. Following only some aspects of the treatment plan would make the individual partially adherent where adherence is a continuous variable. [111]

Adherence can be measured quantitatively or qualitatively, **but there is no single gold standard to measure adherence** as individual treatment adherence measures have their strengths and limitations. [97] Knowing the benefits and limitations of various measures, practitioners can strategically combine numerous measurement methods to more accurately gauge adherence. [67]

The use of multiple measures may most accurately determine treatment adherence.

The following tables **(Table 1a and Table 1b)** provide an overview of methods for measuring treatment adherence. [77, 97, 126, 128, 142, 162]

Table 1a. An overview of subjective measures used to measure medication adherence.

Subjective Validated scales may provide quick and simple measures of adherence, as well as insights into potential causes of non-adherence.	
Self-rated adherence behaviors	**Patients answer questions relating to their adherence behaviors and potential barriers to adherence.**
Pros	· Patients indicating that they have not followed a treatment plan are typically accurate. · Provides real-time adherence behavior feedback
Cons	· Patients denying non-adherence are typically inaccurate. · Can have poor measurement sensitivity or specificity · Subject to communication, interpretation, and literacy barriers or survey design flaws
Practitioner-rated adherence behaviors	**Practitioners evaluate the adherence behaviors of their patients using standard scales or questionnaires.**
Pros	· May remove self-reporting bias · Provides real-time adherence behavior feedback
Cons	· Practitioners tend to overestimate patient adherence. · Can have low measurement sensitivity or specificity · Subject to communication barriers or survey design flaws

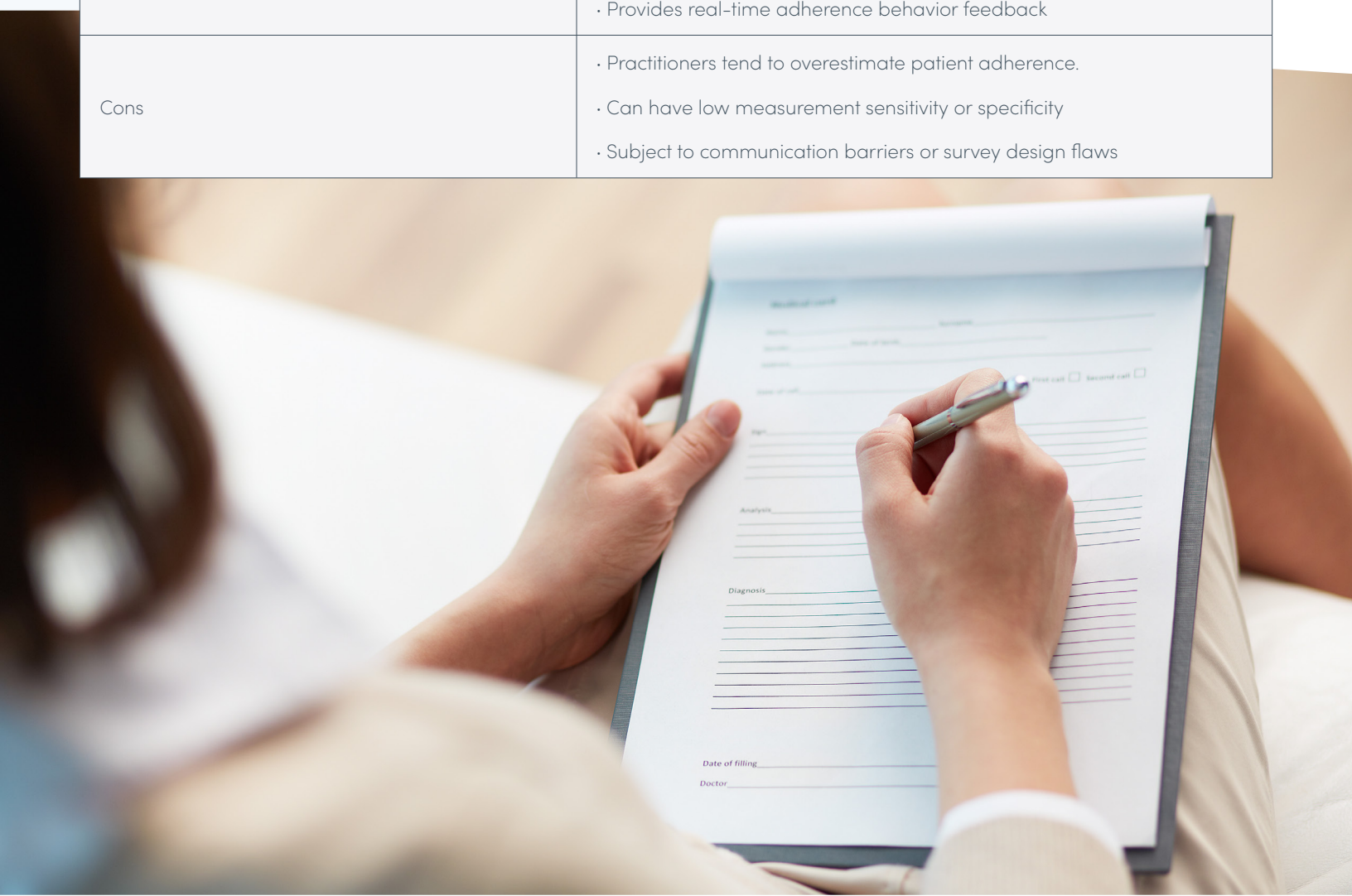


Table 1b. An overview of objective measures used to measure medication adherence.

Objective Provides adherence data with low risk of bias, but can be limited to gaining insight into behaviors related to adherence or for understanding reasons for non-adherence	
Equations of medication adherence	**Mathematical formulae present a straightforward interpretation where adherence is often defined as the use of >80% of doses.**
Pros	· Applies to pharmaceuticals, supplements, or other treatments that use a discrete and planned number of treatment units · Avoids problems of reporting or subjective evaluation bias
Cons	· Overestimation/underestimation of adherence may occur. · Assumes patient actually used the treatment as prescribed · Some do not account for gaps between refills or surpluses of previously available medication. · Determination of adherence can be arbitrary (i.e., >80%) · Does not provide qualitative treatment information, including adherence to dose timing, the handling of missed doses, the reasons for non-adherence, etc.
Electronic medication containers	**Records time and date of when the medication container is opened/ accessed and can send data to practitioner databases**
Pros	· Higher accuracy than other measures such as pill counts (i.e., lower ability to skew adherence patterns/data) · Data on non-adherence sporadicity or consistency with real-time monitoring/feedback on adherence behaviors · Reminds patient to use or refill prescriptions
Cons	· Expensive and may be relatively bulky · Assumes patient actually used the treatment as prescribed · Constant surveillance may cause additional anxiety/stress. · Overestimation of adherence may occur with accidental container opening.

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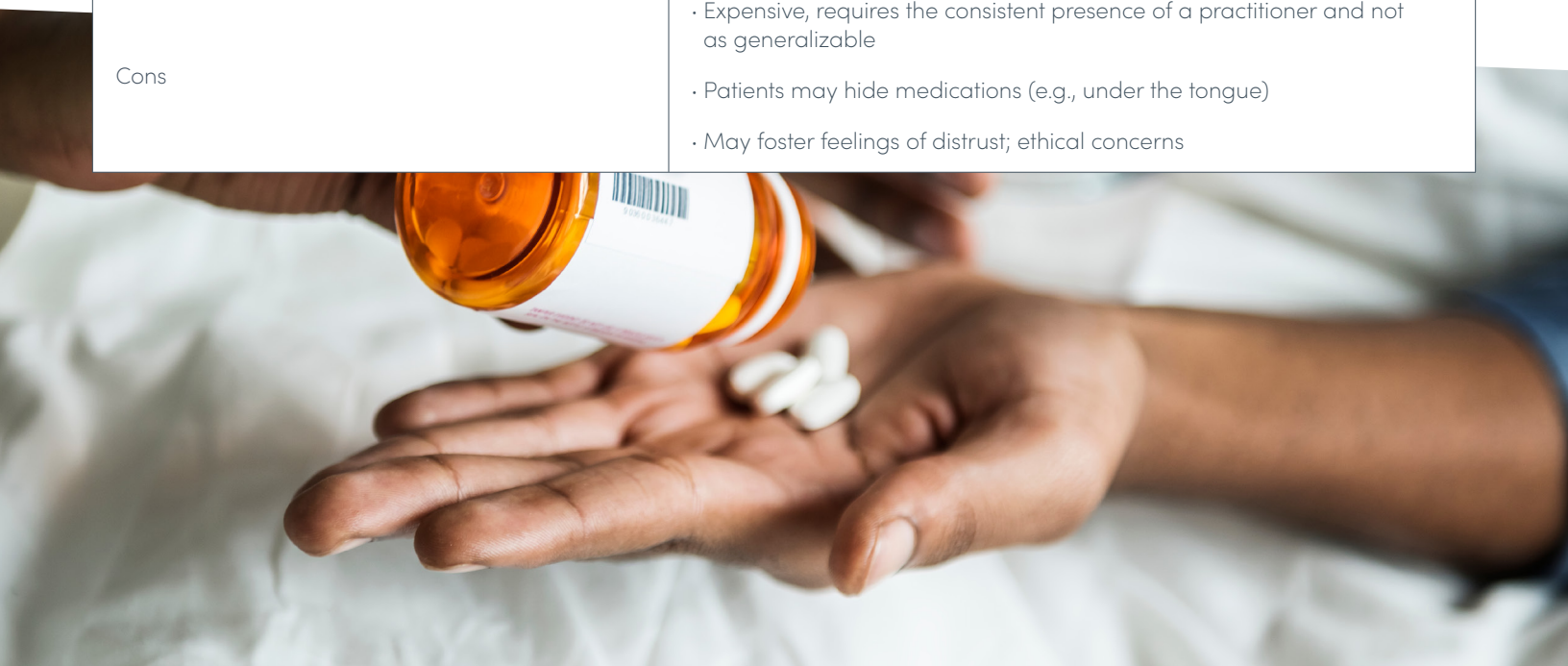
Dispensary databases & EHRs	**Centralized systems or electronic health records (EHR) can manage patients, schedule, create prescriptions, record prescription fill and refill data, observe insurance claims, etc.**
Pros	· Records whether treatment plans are filled, refilled, or prematurely halted, and can provide multi-therapy adherence data · May identify/target patients at high risk of non-adherence
Cons	· Does not provide qualitative treatment information and assumes that treatment was actually used as prescribed · Data can be limited by non-synchronized dispensaries. · May underestimate adherence if medication is acquired outside of the centralized database or not verified
Biochemical measures	**Biomarkers that provide evidence of use of the prescribed treatment; compares standard responses or pharmacokinetic data with the observed response from the patient (e.g., blood/urinary measures, biopsies to seek dyed indicators)**
Pros	· The presence of metabolites or other biomarkers in the body may provide a direct measure of engagement.
Cons	· Factors may skew the interpretation of adherence (e.g., drug-interactions, differences in pharmacokinetics). · Invasive
Directly observed therapy	**Whereby a practitioner is present to administer or supervise the patient's administration of a treatment**
Pros	· Very accurate measure; low risk of mismeasurement
Cons	· Expensive, requires the consistent presence of a practitioner and not as generalizable · Patients may hide medications (e.g., under the tongue) · May foster feelings of distrust; ethical concerns



Five examples of some of the more commonly used and validated self-report questionnaires for medication adherence include: [97, 125]

- The 8-item Morisky Medication Adherence Scale (MMAS-8) [93, 117, 118, 173]
- The Brief Medication Questionnaire [156]
- The Hill-Bone Compliance Scale [84, 98]
- The Medication Adherence Rating Scale (MARS) [65, 72, 160]
- The Self-efficacy for Appropriate Medication Use Scale (SEAMS) [138]

It is important to note, regardless of treatment regimen, that limitations in measurement methods and variance in how adherence is defined are also pervasive across the literature for physical activity and exercise, [9, 49, 103, 105, 133] diets, [25, 39, 50, 62, 69, 91, 94, 121, 179] and complementary and alternative medicines, including supplements. [47, 66, 80, 108, 161, 164]

Physical activity and exercise adherence measures

Questionnaires	**Measures:**
Exercise diaries	Frequency
Session attendance	Duration
Accelerometers	Intensity
Heart rate monitors	Type
Direct observation	Progression

Diet adherence measures

Weighing food containers	**Specific diet questionnaires:**
Anthropometrics	Mediterranean
Stool testing	DASH
24-h urine testing	Gluten-free

Rates of adherence

Broadly speaking, **rates of adherence to the treatment of chronic disease are approximately 50%.** This is a widely cited statistic regardless of whether regimens are based on conventional medicines, targeted lifestyle factors including diet or physical activity and exercise, or complementary and alternative therapies, including supplements.

Medication adherence

Approximately **15 to 30% of new prescriptions (i.e., primary adherence) are never filled.** [22, 54, 55, 59, 168] Ultimately, a lack of adherence within this context is indicative of the existence of a gap between what occurs before, during, or immediately after a medical consultation and the point at which a prescription is either initially filled or not. [77, 170]

15 to 30%
Average rate of non-adherence to new treatment

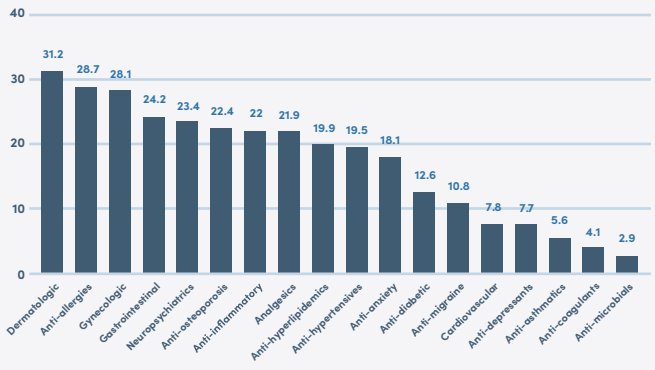
50%
Average rate of non-adherence to the treatment of chronic disease

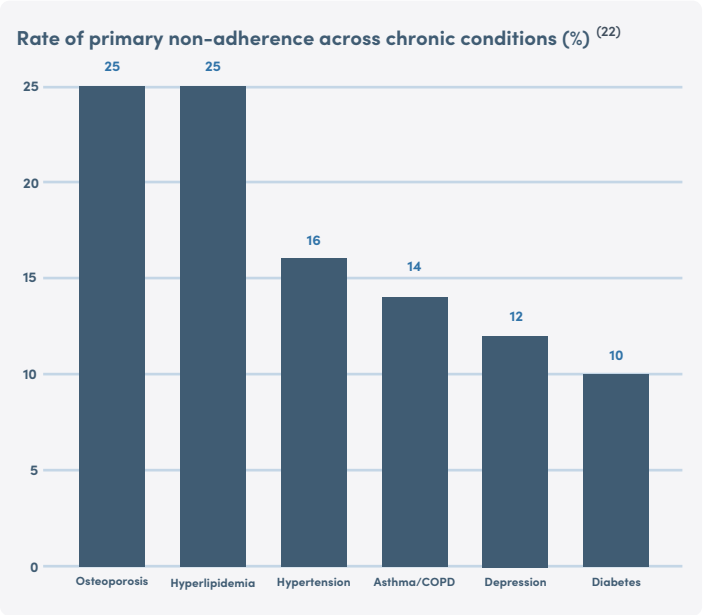
Adherence to chronic disease treatments is cited to be approximately 50% (ranging from 40 to 60%) and mainly refers to secondary adherence within the implementation phase. [15, 87, 123, 128, 142, 154] Even in clinical trials for chronic disease, where patients receive more attention within controlled environments, adherence still only improves to 43 to 78%. [43, 86, 128]

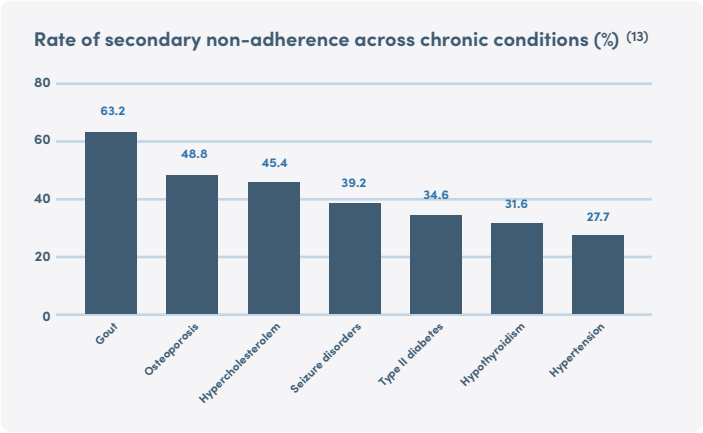
Other analyses have reported primary medication non-adherence data using electronic prescribing transactions or pharmacy claims (below).

Additional analyses have been conducted to predict the likelihood of non-adherence between different drug classes of therapies, such as oral diabetic, [110] anti-hypertensives, [102] and statin medications. [63]

Rate of primary non-adherence to various medication classes (%) [55, 150]







Condition-specific rates of adherence

Adherence rates within **acute conditions** are considered **higher than** those of **chronic disease**, as adherence rates substantially drop within the first six months of treatment. (19, 71, 142, 165) Within the realm of chronic disease management, adherence appears to vary widely based on particular conditions.

Adherence rates drop substantially within

6 months

For example, a meta-analysis, comprising data from 519,971 patients compared **primary medication non-adherence rates** using prescription fill data over the course of one year, across six conditions (see figure above). (22)

Concerning **secondary non-adherence**, a longitudinal study with 706,032 patients using medication possession ratios exceeding 80% (drawn from insurance claim data) compared rates of non-adherence between seven conditions over one year (see figure on the right). (13)

Adherence to physical activity and exercise recommendations

Studies on adherence to physical activity or exercise also commonly refer to the definition provided in the WHO's report, which states, "the extent to which a person's behavior–taking medication, following a diet, and executing lifestyle changes–corresponds with agreed recommendations from a healthcare provider," (142) despite the report's focus on pharmacological adherence. However, **many studies refer to other definitions or do not explicitly define adherence at all.** (9) Specifically applied to physical activity and exercise, some iterations add to the WHO's report by further capturing the **extent to which prescribed intensity, duration, and frequency of physical activity and exercise is accurately performed.** (57)

As shown in the following infographics, low rates of adherence to physical activity guidelines are widely problematic. Low rates of exercise adherence are also extensively observed across states of chronic disease.

50% **of adults** **75%** **of children**

do not meet recommended aerobic physical activity guidelines (85)

36%

of Americans are aware of nationally recognized physical activity guidelines

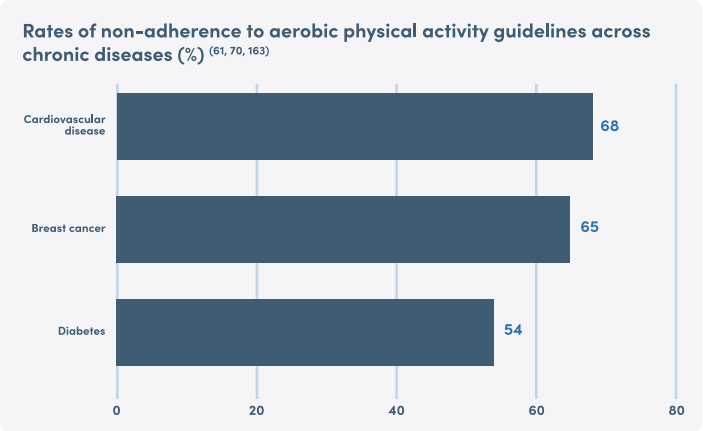
1% of Americans are knowledgeable on the topic (79)

50%

of individuals discontinue from a prescribed exercise regimen within **six months** (105)

23%

of individuals do not adhere to prescribed exercise regimens lasting three months, even in controlled clinical or home-based settings (16)



Adherence to dietary recommendations

Compliance with recommended diets or healthy nutrition plans also falls within the WHO's definition of adherence. Studies within the realm of diet and nutrition refer to the WHO's estimation that **50% of individuals are broadly non-adherent** to their treatment plans. (50, 142)

It may be important to note that although there is **limited evidence to compare adherence rates between personalized diets and standardized diets, there is some evidence that personalized diets may be more effective.** For example, patients with type II diabetes mellitus who received standardized app feedback about the total intake of calories and dietary fat over the course of three months were shown to have lower adherence each month than a group of patients who received personalized feedback on total caloric intake and predicted glycemic scores based on their specific meals. (134) Similarly, scores reflecting adherence to the Mediterranean diet were greater in participants who received personalized nutrition advice, particularly when this was combined with advice based on genetic testing, compared to individuals who received standard dietary advice. (107)

Adherence to complementary and alternative medicine

There is very little information directly comparing broad adherence rates between conventional care and complementary and alternative medicine or integrative medicine therapies such as supplements. One systematic review indicated that **adherence to herbal therapies and other remedies was also approximately 50%.** (45) Overall, regardless of the medical model, non-adherence is described as a "universal" issue. (44)

Researchers and clinicians should not discount the possibility of underlying influential differences between supplements and pharmaceuticals that may lead to dissimilarities in low adherence risk. There may be inherent behavioral differences between individuals actively seeking to manage their health through supplementation (11) as opposed to conventional approaches. For example, inherent motivations for the use of supplements may influence adherence, suggesting that there may be an association between the **self-determined use** of supplements (independent from any advice provided by a practitioner) **and an inherent health-seeking behavior.**

Furthermore, **supplement users are more likely to pursue health and wellness-related characteristics or behaviors,** including wholesome nutritional patterns, increased levels of regular exercise, regulation of healthy body weights, and lower rates of alcohol and tobacco use, and are more likely to have health insurance. (11, 42) As widely described in health promotion literature, intrinsic motivation is associated with both initial engagement of health behaviors and long-term adherence. (58)

23%

of individuals indicated that their use of supplements was based on recommendations from a practitioner (11)

However, differences in adherence to supplements compared with conventional medicines may be attributed to reasons other than internal motivations. For example, patients with high cholesterol have been shown to be 30% more likely to persistently use supplements for two years compared to statins. (26) Meriva®-formulated curcumin products have also shown greater adherence levels than conventional analgesics. (41) Explanations for this difference may include greater perception of long-term safety, lower cost for its relative efficacy, or reduced prevalence of side effects.

Much of the literature has focused on whether CAM improves or reduces the rate of adherence to conventional medicines; however, this remains inconclusive. (46, 88, 92, 124, 132, 140, 176) For example, some studies have shown that CAM has been associated with lower rates of adherence to prescribed conventional medication, indicating that **the use of supplements can also be a negative modifier of conventional medical adherence.** Possible reasons may include individual beliefs, patient preferences, substituting modes of care, or costs of therapy. (51, 92)

In some cases, concomitant use of supplements can also potentially reduce the risk of a conventional therapy's adverse effects, thereby reducing the likelihood of premature treatment discontinuation. (24, 116) Unfortunately, patients also often elect not to disclose their use of complementary and alternative medicines to their practitioners, leading to the possibility of drug-supplement interactions and/or side effects. (3, 35, 56) Possible drug-drug, drug-supplement, and drug-food interactions have the potential to lead to higher rates of non-adherence. (172)

Practitioner-related adherence

Treatment adherence is directly linked with practitioner factors, though this is often overlooked compared with patient-related factors. The mere temporal proximity of a clinical appointment with a practitioner has been shown to affect treatment adherence. **Adherence rates generally decline with time** between check-ins. [115]

White coat adherence:

Higher observed adherence just before or immediately after an appointment

Adherence rates may vary by practitioner modality or specialty, although evidence is limited. For example, primary care providers or general practitioners may have less time available to address factors related to non-adherence, while other practitioners may be able to dedicate more time to navigating patient behavioral barriers. [119, 135]

Rates of medication adherence are often described to be similar between practitioner designations. One meta-analysis showed that physicians, pharmacists, and nurses had similar patient medication adherence rates. [174] Also, nurse practitioners and primary care practitioners (PCPs) had similar adherence rates for anti-diabetic medications, renin-angiotensin system antagonists, and statins. [119]

In general, **the integration of multiple practitioner designations, such as pharmacists, dieticians, or health coaches, into patient care improves adherence and patient health outcomes.** [14, 23, 100, 137, 144, 176]

Interventions for improving medication adherence

One of the most widely studied topics related to adherence is the efficacy of interventions to improve medication adherence. Intervention strategies generally target a specific aspect of adherence (see table). [175]

Strategy or approach	Target or area of focus
Attitudinal	Patient beliefs, motivations, or emotions
Behavioral	Patient behaviors
Educational/cognitive	Patient knowledge of treatment, conditions, and importance of adherence
Multifaceted	Incorporates two or more interventions from different classifications
Psychosocial	Social circles or communities
Rewards	Positive or negative reinforcement for adherence
Structural	Healthcare system, practitioners, policies, or other systemic factors
Technical	Aspects of the treatment itself

Interventions to improve adherence typically have small effect sizes, are transient, [38] and are relatively similar across conditions. [28, 29, 31, 120, 130, 32, 38, 130]

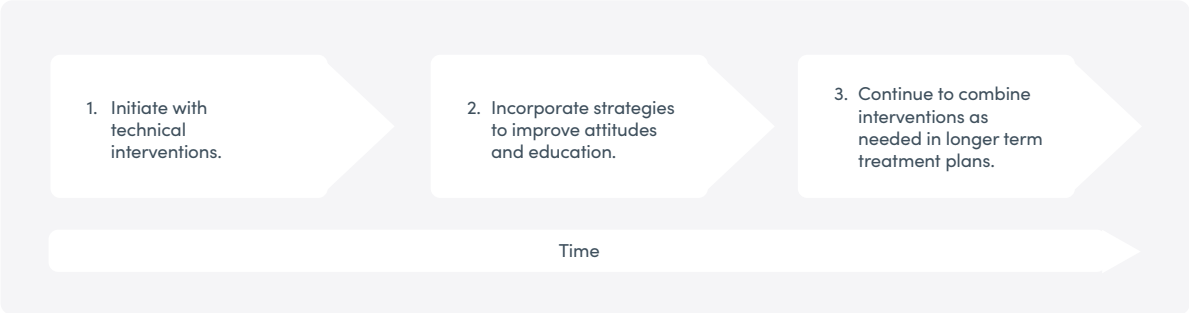
Technical interventions have been shown to provide consistent and reliable benefits to adherence, at least across brief time periods, while **attitudinal and educational strategies were found to increase adherence over time in longer interventions up to ten months.** However, multifaceted interventions were required to continue to improve adherence past this time point. [175]

4 to 14%

Potential average improvement in adherence with interventions [32, 38, 130]

1%

Potential reduction in adherence-improving efficacy of interventions each month [38]



A recent umbrella review identified a few key interventions that have been shown to improve medication adherence across a variety of population groups. **It was determined that the top interventions to improve medication adherence were dose simplification, patient education, electronic reminders, and cost reduction/rewards provision.** [4]

Dose simplification

How:

- Reduce dose frequency [28, 29, 88]
- Use sustained-release formulations [88]
- Suggest combination pills or multi-ingredient formulations [28, 95]
- Suggest products with compartmentalized packaging [28, 29, 30]

Adherence:

- **13 to 36%** via daily dose vs. twice per day [143]
- **22 to 41%** via daily dose vs. thrice per day [143]
- **5%** with combination pill vs. individual pills [95]
- **3%** with sustained-release formulations, **10%** more days with correct dosing vs. regular-release [88]
- Packaging strategies commonly reported to improve adherence, but may be inconsistent [28, 29, 30]

Electronic reminders

How:

- Suggest text messages or other automated cues set to specific dose times via applications [159, 167]
- Personalize texts or use two-way communication [159]
- Consider electronic packaging devices that provide real-time dose use and feedback data [21, 90, 158]

Adherence:

- **18 to 22%** with mobile devices and reduces likelihood of missing appointments by **10%** [76, 78]
- In **40 to 65%** of trials using mobile device reminders [6, 76, 78, 159]
- **10 to 20%** using strategies with feedback [38, 147, 166]
- Electronic packaging strategies commonly reported to improve adherence, but may vary [112]

Patient education

How:

- Provide verbal or written content tailored to the specific condition or barriers to adherence [168, 169, 171]
- Use information leaflets to improve health literacy [155]
- Provide education on how to self-monitor and self-manage the condition [73, 171]

Adherence:

- **16% vs. 10%** among strategies without education [38]
- Education strategies may need to be combined with other interventions to be optimized [34, 36, 73, 175]

Cost reduction and rewards

How:

- Support value-based insurance designs, which reduce costs for highly-effective treatment vs. less effective treatments [2, 89, 101, 148, 157]
- Explore financial reward options (e.g., discounts, loss of percentages of "financial bonuses" for each lapse in adherence) [37, 131]

Adherence:

- Up to **14%** with value-based insurance designs [2, 89, 101, 157]
- With reduced out-of-pocket expenses [89, 101, 109, 148, 168]
- Financial reward strategies may have moderate to large effects on adherence, but may not extend beyond the incentivization period [37, 131]
- Greater frequency of rewards may be more effective than less frequent (at same value) [131]

Interventions that target practitioners are also effective, particularly if they incorporate more than one of the following: [32]

- **Education** (e.g., uncovering barriers and finding solutions, improve their patient's adherence knowledge, and using adherence checklists)
- **Communication** (e.g., active listening, asking adherence-related questions, motivational interviewing, and supportive communication)
- **Assessment and monitoring** (e.g., using monitoring systems, pharmacy refill data, asking patients about adherence and recording answers)
- **The therapeutic alliance/ relationship** (e.g., health agreement negotiations)
- **Integration of care and coordination between practitioners**
- **Increasing time with patients and the continuity of care**
- **Improving access to providers** (e.g., physical proximity to patients or provision of telehealth)

5%

Improvement in patient adherence with practitioner-targeted interventions

Motivational interviewing is a communication technique that may improve medication adherence. [146] It helps guide patients by identifying and focusing on the patient's own intrinsic motivations to improve health. [129, 182] Motivational interviewing uses themes that recognize the **partnership** with the patient, **accept** and value the patient's perspective and efforts, provide **compassion** to reinforce healthy behaviors, and **evoke** the patient's own understanding and knowledge of their behavior rather than imposing such behaviors. For example, practitioners are encouraged to ask open-ended questions, make affirmations to encourage the patient, give reflections to challenge deeper thought about the behavior, and provide summaries to allow for simple understanding. [74] Motivational interviewing is just one example of a strategy for improving behavioral change overall and will be further explored as part of Fullscript's treatment adherence research program.

12%

Improvement in patient adherence with practitioner-targeted communication interventions [181]

17%

Improvement in patient adherence when practitioners are trained in motivational interviewing [129]

Part two

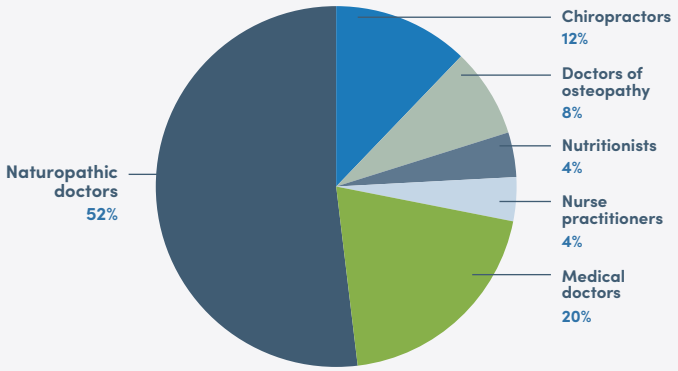
Fullscript practitioner insights

In order to add to current understandings of treatment adherence from the literature, two interview-based studies and a survey were conducted with Fullscript practitioners to gain insights on patient adherence to supplement recommendations made through the Fullscript platform.

Practitioners with low and high adherence rates

A total of 25 interviews were conducted with practitioners demonstrating both high (n=16) and low (n=9) treatment adherence rates (TAR). High TAR was defined as having more than 70% of patients order every supplement from their first recommended treatment plan, whereas low TAR was defined as less than 45%. To qualify for an interview or survey, practitioners were required to meet the respective TAR threshold and be an active Fullscript user, which was defined as having more than five patient orders placed through Fullscript over the last six weeks. In addition, the invitation list consisted of 70% of Fullscript's primary, licensed modalities (i.e., chiropractors, naturopathic doctors, doctors of osteopathy, medical doctors, nurse practitioners) and 30% secondary and/or non-licensed modalities (e.g., dietitians, nutritionists, health coaches, etc.).

Breakdown of practitioner modality in adherence interviews

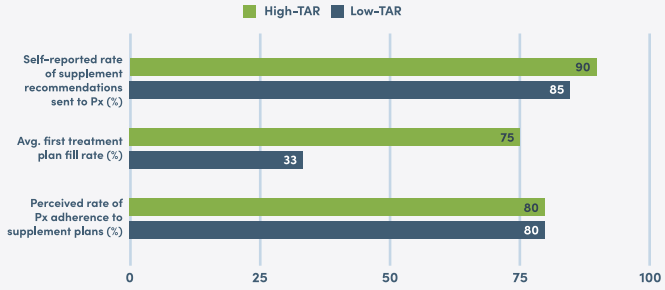


Interview results

Practitioner prescribing behaviors (i.e., the average number of monthly treatment plans written for patients and the self-reported rate of supplement recommendations sent to patients) and **adherence statistics** (i.e., the average first fill rate for treatment plans and the perceived rate of patient adherence to these plans) were determined and stratified by high-TAR and low-TAR practitioners.

Practitioners were asked about the perceived or observed factors that facilitate or create barriers to adherence and were asked to provide strategies that they use to overcome their patient's barriers to adherence.

Fullscript practitioners' treatment plan writing behaviors and adherence

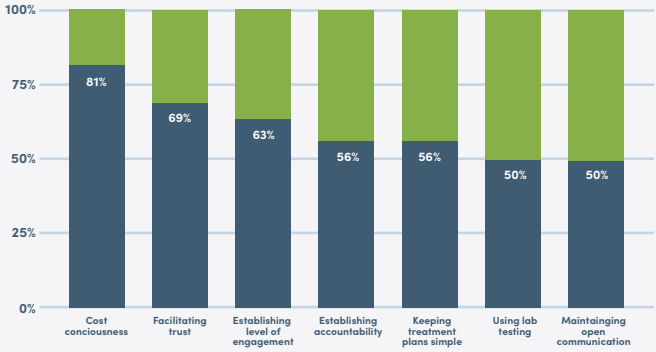


14.41
Ave. number of monthly treatment plans written for high-TAR

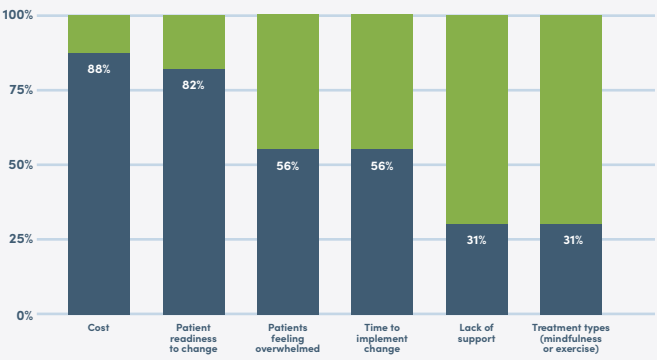
21.43
Ave. number of monthly treatment plans written for low-TAR

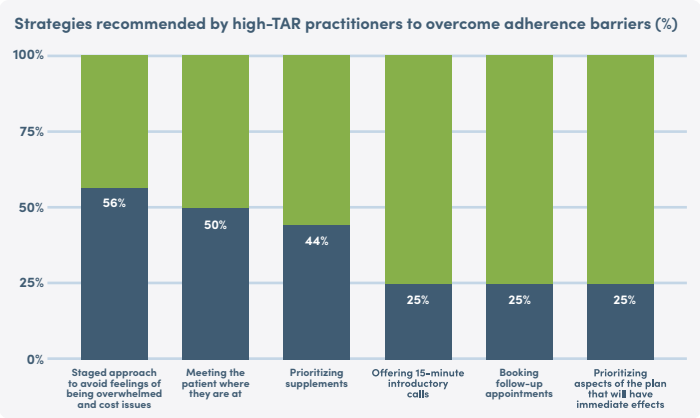
The results were as follows for **high-TAR practitioners**:

Facilitators of adherence from high-TAR practitioners (%)



Barriers to adherence from high-TAR practitioners (%)





For **low-TAR practitioners**, the results were as follows.

Seven out of nine (7/9; 78%) practitioners mentioned that **establishing trust** is a primary best practice for optimizing adherence. Forming a strong and trusting relationship helps to put the patient at the center of care, leading to a feeling of healthcare ownership. **Cost** was again identified (8/9; 89%) as a primary barrier to adherence, citing that supplements are costly and can take a while to be effective. **Readiness to change** was the second prominent barrier (7/9; 78%) and increased the likelihood that cost will prevent the patient from buying the recommended supplements.

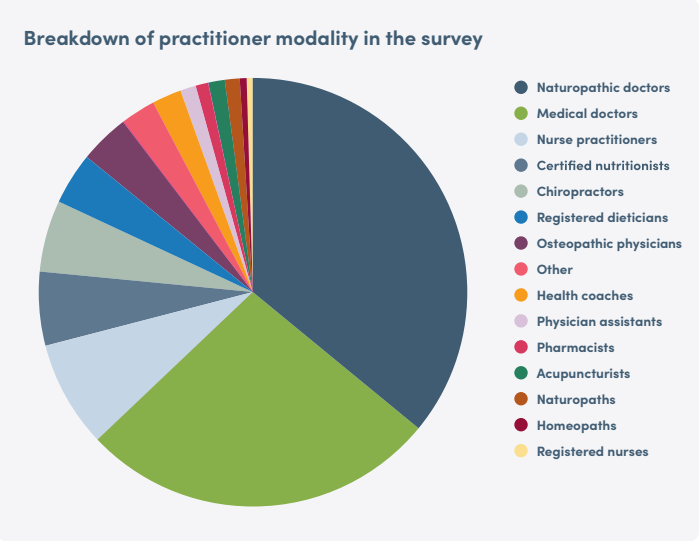
Similar to the high-TAR practitioners, low-TAR practitioners (6/9; 67%) also supported the use of a **"staged" approach** to encourage adherence. One practitioner phrased it as "introducing one piece at a time to help the patient feel in control instead of feeling overwhelmed." Low-TAR practitioners also believed that having evidence and open communication were important strategies to helping with adherence.

Expanding insights with a practitioner survey

To expand on our interview findings, a survey was conducted to gather insights from a larger number of practitioners and to confirm suspected themes arising from the interview process. A total of 185 survey responses were received from both high-TAR practitioners (n=21) and low-TAR practitioners (n=83). The remainder of respondents (n=81) fell between the 45% and 65% adherence range. Due to the low sample from high-TAR practitioners, it was not possible to develop formal conclusions on the significant differences between these groups. However, some assumptions are reviewed in the Discussion section below.

Survey questions incorporated aspects of the following:

- Number of patients seen per week and whether they are prescribed and/or purchase supplements
- How/whether adherence is measured and whether it is a primary concern
- The main barriers to adherence and the actions taken to mitigate them
- Desired adherence features for the platform



Survey results

The following figures show practitioners' prescribing behaviors and adherence statistics from the total survey sample.

46%
Average first fill rate from total survey sample

77%
Average rate of patients receiving supplement recommendations

65%
Average rate of patients ordering at least one supplement off of their first treatment plan

82%
Rate of practitioners perceiving that their patients order the supplement recommendations

77%
Rate of practitioners perceiving that their patients take the supplements as recommended

Other findings related to adherence behaviors include:

>80%
of practitioners learn about their patients' adherence through follow-ups or in appointment conversations

>75%
of practitioners believe that encouraging adherence is a primary concern

69%
of practitioners actively take steps to improve adherence rates

Single most important barrier impeding adherence (% of respondents)	
Cost	29.7%
Readiness to change	15.2%
Overwhelmed by the treatment plan	12.0%
Not seeing immediate results	10.3%
Change in routine	9.2%

Key strategies to improve adherence (% respondents frequently or always use)	
Book follow-up appointments at end of visit	93.5%
Use lab results to explain treatment plans	91.3%
Use a staged approach for treatment plans	85.9%
Communication available between appointments	88.5%

Discussion

Our research sought to elicit strategies and skills that can help improve treatment adherence in integrative medicine. Adherence is a primary concern for integrative and functional medicine practitioners, and our findings have identified several common practices that can help to improve adherence.

Our findings concluded that **cost is the primary barrier to adherence,** and it may be a difficult one to overcome. In integrative medicine, many patients do not have insurance coverage or choose to pay out of pocket. Due to the severity or chronicity of their health concerns, patients often engage with numerous different practitioners to find solutions, which only further increases treatment costs. Practitioners in both low- and high-TAR groups cited **staged treatment plans** and being realistic with patients as key strategies to increase the likelihood of patient adherence. **Setting goals** during the first few appointments that are in line with the patient's financial restrictions were also perceived as crucial for success.

Another main barrier was **feeling overwhelmed** with the treatment plan. This feeling of being overwhelmed may be related to the patient's **readiness to change,** a top-rated barrier identified in the survey. If a patient is not ready or not committed to change, alterations to their diet or exercise routines may seem more challenging. Practitioner respondents advocated having a variety of options and **"meeting the patient where they are"** to overcome feelings of being overwhelmed or not ready.

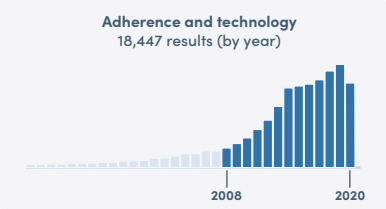
The key best practice emphasized by both high- and low-TAR practitioners was to **establish trust** with the patient. Establishing a trusting relationship may mean that patients will trust the practitioner's expertise and recommendations and could be more likely to move ahead with the treatment plan. Practitioners used **open communication**—including in many cases, offering a complimentary introductory appointment—and an **evidence-based approach** (e.g., lab testing) to help build and maintain trust.

Interestingly, there were many similarities between high- and low-TAR practitioners regarding what they felt were important considerations and barriers of patient adherence, which may suggest:

- There are practitioner-related differences in implementing these adherence-improving strategies or interventions that need further investigation.
- Differences in patient characteristics (e.g., demographics, behaviors, conditions, etc.) may impact TAR.
- Limitations in the accuracy of our internal data to assess adherence based on supplement prescribing and ordering behavior

At a first glance, the key strategy of **"keeping treatment plans simple"** is complemented by the Fullscript data on first fill rates and treatment plan size. Generally, we see that higher full fill rates are associated with smaller treatment plans. Though we cannot definitively comment on the cause of the relationship, it is worth exploring in future research. Overall, keeping the treatment plan trimmed to essential supplements is a well-advised strategy based on high-TAR practitioner trends.

Technology has the potential to improve the ways in which interventions are delivered. Though mobile devices and the internet have existed for decades, research taking advantage of these technologies for adherence has only started to expand within the last ten to 15 years.



The multifunctionality of these technologies has provided numerous new streams in which patients can organize, collect, manage, and share personal, medical, and adherence-related data. Innovative technological health platforms, such as Patient Health Records (PHRs), can provide education, personalization, feedback, alerts, gamification, medication management, medical appointment management, diaries, self-monitoring, health condition management, goal setting, health blogging, and integrations with electronic health records and prescribing platforms. [5, 99, 106]

Technologies with the ability to provide **self-monitoring and/or feedback** to users seemed to have the greatest rate of success at improving adherence (82%) compared with the success rate of **education and/or counseling** (39%) or **electronic reminders** (33%). [114] Even in the case where medication adherence may or may not improve with these kinds of technologies, other related factors such as patient-provider communication, self-efficacy, self-management, and knowledge, may still improve. [99, 178]

2x

Greater likelihood of improved adherence when patients use applications that support adherence behaviors [8]

Final thoughts and next steps

With respect to measuring supplement adherence, **unlike prescription pharmaceutical medications, no large, centralized database exists to accurately record and monitor patient use of supplements.** Supplements are not as strictly regulated as pharmaceuticals, are more widely available from multiple sources, and are not as consistently tracked in patient health records. [27, 52] A significant systemic health impact could be made from a health platform that centralizes supplement-consuming behaviors, particularly if details on supplement type, dosage, brand, vendor, regularity of refills, and other adherence-related factors are recorded.

Fullscript has the potential to **lead the development and establishment of a centralized database that acquires adherence information and provides solutions to its practitioners and patients,** a tool that is neither currently available in the field of integrative medicine, nor in the supplement industry as a whole. The current multifunctionality of the platform can provide ample opportunity to educate providers and patients, while measuring, monitoring, and improving treatment adherence.

As with other large administrative databases, this data could be used to explore further research questions and add to the body of evidence on treatment adherence. For example, questions that may be posed include:

- Whether supplement users are more likely to experiment or alter recommended dosing or treatment schedules if supplements are perceived to be natural and/or safe options
- Whether supplements intended for preventative care have lower adherence rates compared those intended for therapeutic care
- Whether patients are more likely to be non-adherent to supplement recommendations on the basis of costs or health insurance coverage
- Whether there are additional interventions available to integrative practitioners to improve patient adherence with non-supplement recommendations such as diet, lifestyle, exercise, etc.

Of course, it is unclear whether improving treatment adherence alone impacts patient-oriented outcomes. Ways of improving the measurement of these outcomes and linking them with adherence rates should be prioritized. Interventions that consider integrative and comprehensive treatment plans (e.g., supplements, diet, behavior/lifestyle, etc.) will also likely optimize benefit and should be explored further.

To expand on our practitioner insights, **next steps should include studies directed towards the day-to-day differences between practitioners experiencing high and low TAR.** The findings of this study demonstrate significant overlap between the two groups, indicating that there are either undiscovered variables at play or differences in the implementation of the mutual key strategies.

As a result of our research, Fullscript has identified and targeted a key knowledge gap in the understanding of treatment adherence in the realm of integrative medicine. With future efforts and through building unique partnerships, **we aim to advance the field of integrative medicine through additional research and interventions that support treatment adherence.** Ultimately, by improving overall patient adherence to comprehensive integrative (not simply supplement-based) treatment plans, we can continue on our mission to change the way that health is prescribed.

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