

Adherence With Oral Anticancer Therapies: Clinical Trial vs Real-world Experiences With a Focus on Prostate Cancer

Celestia S. Higano^{1*} and Jason Hafron²

¹Department of Urologic Sciences, University of British Columbia, Gordon & Leslie Diamond Health Care Centre, Vancouver, British Columbia, Canada

²Michigan Institute of Urology, Troy, Michigan

Purpose: In this review, we address adherence rates in clinical settings, barriers to compliance with dosing schedules, and potential strategies to overcome challenges in maintaining high levels of adherence.

Materials and Methods: Four studies reporting real-world adherence to prostate cancer medications, 52 studies describing barriers to adherence, and 16 studies on methods to minimize poor adherence were reviewed.

Results: Mean nonadherence rates of 25% to 51% have been identified in prostate cancer patients prescribed oral therapies, with higher rates in older patients. An extensive review of prostate cancer patients receiving gonadotropin hormone-releasing hormone agonist injections found an overall non-adherence rate of over 27%. Patients may encounter barriers to complying with dosing instructions related to the medication (eg, complex dosing schedules, the total burden of medication management, fasting or dietary requirements, high medication costs, adverse effects, and drug-drug interactions). Barriers may also be related to patient-specific factors (eg, suboptimal education regarding the importance of adherence, physical limitations and cognitive decline associated with advancing age, living alone without a care partner, high symptom burden, needle phobia, and comorbid mental disorders). Interventions to improve dosing adherence may include automated reminders, treatment diaries, educational materials, and the involvement of patients, family members, care partners, and health care teams.

Conclusions: Many oral anticancer medications improve survival in men with prostate cancer, and therefore it is vital to establish good adherence by understanding the pitfalls that patients may encounter. In situations where both oral and injectable drugs are interchangeable, injections of long-acting drugs lead to fewer opportunities for dosing nonadherence than oral therapies. In contrast, oral medicines do not require scheduling for injections and travel for injection appointments. Therefore, maximizing adherence to all treatment regimens will reduce the chance of efficacy failures and likely lead to improved clinical outcomes.

Key Words: medication adherence; administration, oral; antineoplastic agents; prostatic neoplasms; androgen antagonists

IMPORTANCE OF DOSING ADHERENCE

Therapeutic efficacy requires consistent administration of specific drug doses at intervals listed in the labeling. Clinicians can verify that injections

administered in their clinics are timely, however confirming whether patients are taking oral medications correctly can be more challenging. Adherence is defined as the extent to which a person's behaviors, eg, taking medication,

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Ethics Statement: In lieu of a formal ethics committee, the principles of the Helsinki Declaration were followed.

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*Correspondence: Department of Urologic Sciences, University of British Columbia, Gordon & Leslie Diamond Health Care Centre, Level 6, 2775 Laurel St, Vancouver, BC, Canada (telephone: 206-972-7952; email: madronaoncology@gmail.com).

following a diet, and executing lifestyle changes, etc, correspond with provider recommendations. Inadequate adherence to oral therapies in elderly patients has resulted in poor clinical outcomes,¹ such as earlier disease progression. A study in chronically ill geriatric patients found good adherence in 55% of patients aged 60-70 years, but only 26% for patients aged 71-80 years, and 0% for patients over 81 years.² Therefore, increasing age is a significant risk factor for incorrect medication administration (Figure 1). Medication nonadherence can also have a significant negative economic impact due to medication waste, increased emergency department costs, and increased hospitalization costs.

As new oral anticancer agents are approved and prescribed, clinicians should have an awareness of potential noncompliance with labeled instructions and consequent loss of efficacy.³ Given their often narrow therapeutic margins, high-cost, efficacy benefits, and significant side effects,³ adherence to recommended dosing schedules for oral anticancer drugs is critical.

Androgen deprivation therapy (ADT), including gonadotropin hormone-releasing hormone (GnRH) agonists and antagonists, inhibits prostate cancer (PC) tumor growth by suppressing testosterone (T) to castration levels. Decreased efficacy due to deviation from labeled dosing schedules may have serious negative clinical consequences. Continuous T suppression could be required for many years, including throughout the castration-resistant phase of therapy. The recent approvals of an oral ADT (relugolix) and androgen pathway inhibitors such as abiraterone and enzalutamide have raised concerns about the risk of non-adherence and the consequent negative clinical impact. Nonadherence to PC medications (eg, missed doses of orals or delayed dosing of an injectable drug) increases the risk that drug concentrations will fall below the levels required for effective T suppression, thus increasing the risk of transient spikes in T or escapes above castration levels. Data from a recent publication suggest that T levels will rebound much faster following treatment cessation with an oral GnRH antagonist than an injectable agonist,⁴ so the risk of T escape, and consequent loss of efficacy, due to nonadherence may be higher for the oral drug.

To bring this subject to the attention of clinicians, this review summarizes adherence data for commonly prescribed PC oral and injectable therapies, describes barriers to dosing per labeled instructions, and recommends ways to increase adherence to maximize the chance for favorable clinical outcomes.

MATERIALS AND METHODS

In selecting studies for this review, we searched PubMed, Embase, and CINAHL. Subsequently, all the reference

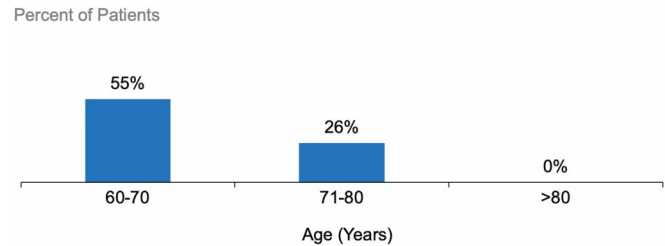


Figure 1. Good adherence to oral medications by age group. Elderly patients (n=251) aged >60 years with chronic illnesses receiving long-term medications for more than 6 months were prospectively evaluated for medication adherence. All prescribed medications were oral (eg, antidiabetics, calcium channel blockers, angiotensin receptor blockers) except insulin and inhalation anti-asthmatics. Good adherence was defined as reaching 16-20 out of 20 points assessed by a pretested structured questionnaire as per the modified Morisky Adherence Scale. Reprinted with permission from Cramer 1990;150:1509.⁶

lists of the included studies were examined manually to identify additional relevant studies.

Inclusion criteria guided the search and selection of the items: English language; PC population; clinical studies reporting medication adherence; real-world studies reporting medication adherence; barriers to medication adherence; interventions to improve adherence (Table 1).

The titles and the abstracts were reviewed. If the abstracts reported PC medication rates, barriers to adherence, or interventions to improve adherence, full texts were read and if the pre-established eligibility criteria were met, they were included in the review. Of the thousands of publications captured in the initial search, 6 studies reporting real-world adherence to PC medications, 52 studies describing various barriers to adherence, and 16 studies on ways to minimize poor adherence were selected.

Dosing Adherence in Clinical Trials vs Real-world Practice

If adherence were not an issue, oral anticancer medications would be an attractive treatment option for their convenience and ease of administration. Although adherence rates >95% have been reported in clinical trials of oral oncolytics,⁴ these likely do not reflect real-world experience. A recent systematic review on adherence to oral antineoplastic agents revealed that most studies had a high risk of overestimating real-world adherence.⁵ Clinical trial procedures that may improve adherence include frequent monitoring, medication dispenser tracking, and the use of technologies such as

Table 1. Inclusion Criteria

	Inclusion criteria
Initial literature search	<ul style="list-style-type: none"> • English • Prostate cancer population • Search terms: prostate cancer, adherence, medication adherence, persistence, compliance, oral therapies, oral oncolytics, barriers to adherence; interventions to improve adherence
Title and abstract screening	Reported at least 1 of the following: <ul style="list-style-type: none"> • adherence in clinical trials • adherence in real-world practices • barriers to adherence • interventions to improve adherence

Table 2. Strengths and Weaknesses of Methods Evaluating Real-world Dosing Adherence

Method	Examples	Strengths	Weaknesses
Direct	<ul style="list-style-type: none"> • Observation of medication intake⁵¹ • Detection of medication in a biological fluid⁵² 	<ul style="list-style-type: none"> • Accurate⁵² • Increased adherence^{36,37} 	<ul style="list-style-type: none"> • Expensive⁵² • Impractical⁵¹ • Labor intensive^{51,52} • Intrusive⁵¹ • Negatively impacts patients' life with repeated testing⁸
Indirect	<ul style="list-style-type: none"> • Pill count⁸ • Prescription filled⁸ • Self-report⁸ 	<ul style="list-style-type: none"> • Less expensive^{8,53} • More practical^{8,53} 	<ul style="list-style-type: none"> • Less accurate • Potential overestimation⁵⁴ • Influenced by external factors (eg, care partner's presence)

smart bottles, electronic patient diaries with alarms, and telephone reminders. There is also evidence that trial participation itself significantly improves adherence. Practices that maximize treatment adherence during clinical trials are rarely replicated in real-world clinical settings.

There are direct and indirect methods for assessing real-world dosing adherence (Table 2), which have been shown to overestimate actual adherence.^{6,7} Direct methods are expensive and labor-intensive but more accurate than indirect methods.⁸ Electronic monitoring may improve the accuracy of indirect monitoring. For example, a study compared adherence based on pill counts to data from a “smart bottle” that recorded the precise times the bottle was opened. Adherence was misclassified in 22% of visits, indicating that adherence rates based on pill count (92%-99%) were inaccurate.⁷ However, this method cannot assess actual drug ingestion and partial adherence may not be detected.

Studies of real-world adherence to PC medications indicate that nonadherence occurs for both oral and injectable formulations.⁹⁻¹⁴ Overall, adherence to androgen receptor axis-targeted therapies (eg, abiraterone, enzalutamide) has been reported as high (93%-97%).^{9,10} However, these studies evaluated adherence indirectly using medication possession ratio,^{9,10} which cannot confirm medication ingestion, let alone time of medication ingestion. Therefore, the adherence rates for these drugs as per labeled dosing instructions may be lower than reported. Consistent with data from chronically ill geriatric patients,² nonadherence to oral PC medications was higher in older patients.^{11,12} A large-scale review of electronic medical records from PC patients who received intramuscular and subcutaneous (SC) GnRH agonist injections found 27% nonadherence for both injections.¹³ It is important to note that, due to the extended-release nature of long-acting injections, patients who received late injections were still adherent during the

Table 3. Barriers to Adherence

Barrier	Impact on adherence
Complex dosing schedules	<ul style="list-style-type: none"> • Patients prescribed multiple different medications have reported confusion about what number of pills to take, when to take them, and how many pills they have already taken¹⁶ • Polypharmacy (5 or more) is associated with nonadherence⁵⁵ • Difficult to sustain over extended periods²⁶
Burden of medication management	<ul style="list-style-type: none"> • Responsibility of remembering and choosing to take medications on time each day • Higher stress associated with lower treatment adherence²⁰
Required changes in mealtimes and diet	<ul style="list-style-type: none"> • Diet changes increase the burden of self-management • Patients are confused or scared of the consequences of taking their medications incorrectly
High medication costs	<ul style="list-style-type: none"> • Patients may skip/delay doses to save money⁵⁶
Adverse events	<ul style="list-style-type: none"> • Patients may skip/delay doses to avoid side effects
Drug-Drug interactions	<ul style="list-style-type: none"> • Associated with increased hospitalization costs and increased length of stay⁵⁷ • Confusion in understanding of generic and trade drug names⁵⁸ • Increased complexity of therapy management⁵⁸ and increased risk of adverse events • Patients may self-select over-the-counter drugs and/or herbal supplements that clinicians aren't aware of, which can have serious interactions with prescription medications
Lack of patient education on the importance of adherence	<ul style="list-style-type: none"> • Poor or incomplete understanding of adherence • Misperception regarding the importance of the drug dose and continuity¹⁴ • Patients may have limited language proficiency and/or literacy
Physical and social limitations of advancing age	<ul style="list-style-type: none"> • Discomfort and difficulty with swallowing^{59,60} • Decline in manual dexterity makes it difficult to open pill bottles³³ • Visual impairment makes it difficult to read medication labels • Poor mobility and lack of transportation^{61,62,78} • Impaired cognitive function due to aging (eg, poor memory)⁶³ and/or disease treatment⁶⁴
Living alone and/or lacking a care partner	<ul style="list-style-type: none"> • Lack of reminders⁶⁵ • Confusion about dosing schedule and/or food restrictions • Increased likelihood of depressive symptoms,⁶⁶ which increases the odds of nonadherence⁶⁷
High symptom burden	<ul style="list-style-type: none"> • Patients who report greater symptoms are more likely to engage in both intentional (eg, changing medication dose or stopping medication) and non-intentional (eg, forgetting to take medication) non-adherent behaviors³⁹
Comorbid common mental disorders	<ul style="list-style-type: none"> • Patients with chronic diseases are more likely to have common mental disorders,⁴¹ which negatively impact adherence⁶⁷

labeled dosing period following the previous dose, only when drug release diminished was efficacy affected. These analyses of real-world data show that nonadherence rates for patients treated with oral PC therapies may be higher compared to injections. However, direct comparisons of nonadherence rates should be conducted with caution due to the variety of measures used in making assessments.

Barriers to Dosing Adherence

A systematic review of 79 studies found that annual costs attributed to nonadherence ranged from \$5,271 to \$52,341 per patient, and lower levels of adherence were associated with higher total costs.¹⁵ Complex dosing schedules, the burden of medication management, high medication costs, adverse effects, drug-drug interactions (DDIs), suboptimal education regarding adherence, physical limitations and cognitive decline due to advancing age, living alone without a care partner, high symptom burden, and comorbid mental disorders can all contribute to nonadherence (Table 3).

Complex Dosing Schedules. Patients have reported confusion about the number of pills, when to take them, and forgetting whether pills have already been taken.¹⁶ Polypharmacy is common in older patients with cancer; 80% of patients ≥ 65 years old with newly diagnosed cancer take 5 or more medications concurrently.¹⁷ Complex dosing schedules are also difficult to sustain for extended periods. A systematic review of patients suffering from chronic disease found that less frequent dosing was associated with improved adherence.¹⁸

Burden of Medication Management. Patients prescribed oral medications are responsible for taking them on time every day, and the difficulty of medication management increases with a greater number of pills. Additionally, approximately half of oral anticancer medications have instructions regarding drug intake in relation to eating, as food can impact the absorption of many drugs. In contrast, the patient, clinicians, and clinic staff share responsibility for maintaining adherence to office-administered medications. The patient's failure to schedule or keep appointments and the health care system's inability to provide appointments due to lack of availability are potential barriers to adherence. Even with scheduled appointments, patients risk nonadherence if they do not receive drugs on time. In a retrospective analysis of 22,860 patients with PC treated with luteinizing hormone-releasing hormone agonists, 27%-84% of the injections were late (although just being late, eg, 1-2 days, isn't enough to mean loss of efficacy, especially with SC injections).¹⁹ As higher stress levels are associated with lower adherence,²⁰ clinicians should consider ways to reduce patients' burden of medication management.

Financial Impact. Financial toxicity, which refers to the negative impact of the excess financial strain caused by cancer diagnosis and treatment, can lead to nonadherence. High out-of-pocket contributions may incentivize patients to save money by skipping or splitting doses.²¹ Patients >65 years old were more likely to request cheaper medications than those aged 18-64.²¹ Finance-based physician choices may indirectly affect patients' adherence by preventing them from receiving the medication type that best supports adherence. For example, urologists and oncologists may prefer to prescribe injectable therapies over oral pills because there is available billing for

administering injections in the clinic that does not exist with pills. This choice may support better adherence as patients would be effectively treated for the entire labeled dosing duration, even if a subsequent injection is late. However, suppose clinicians choose to prescribe oral pills because, eg, they are more easily reimbursed by third-party payers. In that case, this could lead to a higher risk of nonadherence and a more significant negative impact due to nonadherence.

Socioeconomic Status and Racial Disparities. Poor adherence has been associated with both lower socioeconomic status and race. First, a nationwide study found that patients with lower household incomes were more likely to be non-adherent and associated with higher mortality.²² Second, racial/ethnic disparities in cost-related medication adherence have been reported among older patients.²³ A cross-sectional national survey of Medicare beneficiaries ≥ 65 years old found that those who are Black or Hispanic were more likely than Whites to report cost-related nonadherence (35%, 37%, and 27%, respectively, $P < .001$).²³ Finally, there are likely socioeconomic and racial disparities in health care access, decreasing medication adherence.²⁴ Thus, patients with lower socioeconomic status and those who are non-White have a higher risk of nonadherence with potentially negative clinical consequences.

Adverse Events. Adverse events (AEs) negatively impact patients' quality of life (QoL), thus increasing nonadherence risk. PC therapies that suppress T will frequently cause AEs such as decreased bone mineral density; metabolic changes such as weight gain, reduced muscle mass, and increased insulin resistance; decreased libido and sexual dysfunction; hot flashes, gynecomastia; reduced testicle size; anemia; and fatigue.²⁵ Additionally, AEs including anemia, hypokalemia, fatigue, and pain have been reported in patients treated with androgen receptor axis-targeted therapies. Nonadherence to ADT can cause T levels to increase and reduce associated AEs thus predisposing to further nonadherence. AE management is essential for improving patients' QoL and encouraging adherence. More frequent clinic visits would increase the likelihood that steps are taken to manage AEs promptly.

AEs may vary depending on the route of administration. For example, visual analog scale scores (0 = "Never," 100 = "Constantly") assessing nausea and vomiting frequency decreased by 11.5 (from 36.5 to 25.0) and 4.8 points (from 5.8 to 1.0), respectively, when patients switched from oral methotrexate to SC injections.

The impact of AEs on adherence may be more significant for patients taking oral medications than those receiving injections as they could skip oral doses to reduce the impact of AEs. In contrast, patients receiving long-acting injections do not have that option. Depot injections ensure that patients receive continuous therapeutic coverage throughout the dosing period without the potential for disruption or discontinuation. However, patients are "locked in" to exposure to the drug once they receive their injection, and do not have the option of stopping treatment should they experience AEs.

DDIs. Interactions with other drugs have been identified as significant barriers to adherence to oral anticancer medications by health care providers and patients.²⁶ DDIs, including those with serious clinical consequences, can also occur when

Table 4. Drug-Drug Interactions of Oral Prostate Cancer Therapies

Therapy ^a	Approval year	Avoid
Enzalutamide (XTANDI)	2012	<ul style="list-style-type: none"> • Strong CYP2C8 inhibitors⁶⁸ • Moderate CYP3A4 or CYP2C8 inducers⁶⁸ • CYP3A4, CYP2C9, and CYP2C19 substrates⁶⁸
Darolutamide (NUBEQA)	2019	<ul style="list-style-type: none"> • Combined P-gp and strong or moderate CYP3A inducers⁶⁹ • Combined p-gp and strong CYP3A inhibitors⁶⁹ • BCRP substrates⁶⁹
Relugolix (ORGOVYX)	2020	<ul style="list-style-type: none"> • P-gp inhibitors⁷⁰ • Combined P-gp and strong CYP3A inducers⁷⁰ • Combined P-gp and moderate CYP3A inhibitor⁷⁰
Abiraterone (ZYTIGA)	2011	<ul style="list-style-type: none"> • CYP2D6 substrates⁷¹
Apalutamide (ERLEADA)	2018	<ul style="list-style-type: none"> • CYP3A4, CYP2C19, CYP2C9, UGT, P-gp, BCRP, or OATP1B1 substrate⁷²

^a Prostate cancer medications such as sipuleucel-T (PROVENGE), radium-223 (XOFIGO), degarelix (FIRMAGON), and GnRH agonists do not have drug interactions listed in the prescribing information.

prescription medications are co-administered with over-the-counter and herbal medicines,^{27,28} which are used by 20% of oncology patients.²⁹ As these nonprescription medications are likely to be self-obtained, clinicians may not be aware that patients are taking them, thus increasing the risk of DDIs that could lead to a lack of efficacy or AEs. Complex DDIs are commonly seen with many PC therapies (Table 4) and have been associated with increased hospitalization costs and length of stay. A study of geriatric patients taking multiple medications found that 26% were taking drug combinations that could result in AEs or reduced therapeutic efficacy due to DDIs.³⁰

Lack of Patient Education on the Importance of Adherence. Patients' poor comprehension of "adherence" may present another barrier to correct dosing. In a survey, almost all patients self-reported high adherence, but only 40% of health care providers believed that most of their patients were truly taking their medications as prescribed; 77% of patients reported nonadherence due to misperceptions regarding the importance of dose level and dose continuity.¹⁴ Taibanguay et al demonstrated that patient education, consisting of 30-minute directed counseling and a disease information pamphlet, significantly improved adherence.³¹ It is essential to recognize that patient education should be an ongoing process with the health care team providing regular follow-up, including calls to patients or caregivers. Patients should also be encouraged to notify their health care team of events following the introduction of new

medications. Moreover, limited language proficiency and literacy can contribute to poor adherence. Visual aids may help patients with communication barriers. Clinicians should improve patient education by proposing counseling sessions, providing brochures during clinic visits, identifying relevant online resources, using professional medical interpreters (not family members or friends) when needed, and employing visual aids.

Physical Limitations and Cognitive Decline Due to Advancing Age. Advancing age has been associated with decreased dosing adherence. One study reported that 49% of PC patients over 65 years were not taking their medications as labeled, compared to 10% of men under 65.¹² The physical impact of aging can affect patients' ability to take their medications consistently in several ways, including difficulty swallowing pills due to dysphagia,³² trouble removing medications from their packaging or bottles because of reduced manual dexterity, tremors, and arthropathies,³³ and inability to read printed dosing instructions.³⁴ Elderly patients may experience decreased ability to move and walk quickly, which could negatively impact their ability to drive safely. Thus, it is difficult for some elderly patients to visit clinics for injections. In this situation, oral medications may be preferred because they can be delivered directly to their homes.

A study in older adults (mean age 80 years) found that nonadherence was 2.5 times more likely in subjects with poor cognitive function compared to normal subjects.³⁵

Table 5. Methods to Reduce Nonadherence

Method	Examples	Strength	Weakness
Automated telecommunications interventions	<ul style="list-style-type: none"> • Short message service (SMS)-based systems⁴⁵ • Voice messages⁷³ • Interactive voice response phone-based platforms⁷⁴ • Smartphone applications⁷⁵ 	<ul style="list-style-type: none"> • Effective if highly tailored to the patients' beliefs and prescription plan⁷⁶ • Scalable • Low cost 	<ul style="list-style-type: none"> • Challenging to implement in the elderly population
Behavioral prompts	<ul style="list-style-type: none"> • Involving patients with health care teams⁷⁷ • Frequent interactions with health care providers⁷⁷ • Reminders to refill medication all support better adherence⁷⁸ 	<ul style="list-style-type: none"> • Improve mood symptoms⁴⁶ • Increase patient involvement in their own care⁷⁸ 	<ul style="list-style-type: none"> • Challenging to implement in everyday clinical practice • Not cost-effective⁷⁵
Self-management	<ul style="list-style-type: none"> • Pill organizer to sort complex medication regimens⁷⁹ 	<ul style="list-style-type: none"> • Cost-effective⁷⁹ 	<ul style="list-style-type: none"> • Exposes medications to environmental factors⁸⁰ • Challenging to remember filling the pillbox • Need to develop a habit to use pillbox daily

Table 6. Pros and Cons of Adherence by Therapy Type

Therapy	Strength	Weakness
Oral	<ul style="list-style-type: none"> • Daily pill is a familiar and common form of medication • Adherence would be high for patients who develop the habit and can manage medication schedule 	<ul style="list-style-type: none"> • Short half-life of oral medications⁴ • Daily dosing required to consistently and reliably maintain T suppression⁸¹ • Instructions may be difficult to understand • Administration of numerous medications at frequent intervals throughout each day and/or at specific times during the day may increase nonadherence.^{82,83}
Injection	<ul style="list-style-type: none"> • Extended-release technologies⁸⁴ • Greater coverage should dosing be delayed⁸⁴ • Unlikely to miss a dose altogether as scheduled and administered by health care provider 	<ul style="list-style-type: none"> • Requires attendance at office • Scheduling challenges • Potential for injection site reactions⁸⁵ • Medication needs to be prepared/reconstituted⁸⁵
Implant		<ul style="list-style-type: none"> • Requires surgery and potentially anesthesia⁸⁶

Patients with cognitive impairment may forget to take their medications, mainly if a care partner is not present to remind them. Conversely, confusion about whether a medication has already been taken has been reported in 30% of patients aged ≥ 40 years with a chronic condition,³⁶ and this can lead to “double dosing” which may have significant adverse consequences for drugs with narrow therapeutic margins such as digoxin. Physicians may be unaware of issues with cognitive impairment in some of their patients. If there are problems with drug adherence, assessment of cognitive function should be considered.

Living Alone or Lacking a Care Partner. Patients who live alone or do not have care partners are at increased risk for nonadherence. It has been reported that 63% of elderly patients who lived alone were nonadherent compared to 53% of those who did not,³⁷ and approximately 50% of caregivers assist elderly patients with medication management. Twenty percent of people over 65 reported having difficulty with medicines and were not able to receive help.³⁸

High Disease Symptom Burden. Symptom severity experienced by patients may affect adherence, as observed in oncology patients with greater symptom burden who were likely to engage in both intentional and nonintentional nonadherent behaviors.³⁹ A study found that patients who reported more severe cancer-related symptoms (eg, fatigue, drowsiness, disturbed sleep, and memory problems) had lower adherence.⁴⁰

Comorbid Common Mental Disorders. Patients with chronic diseases, including PC, are more likely to suffer from mental disorders, which reduces medication adherence. Nakash et al reported that the prevalence of common mental disorders was higher among individuals with active cancer (18.4%) than those without cancer (13.3%).⁴¹ Of the respondents with active cancer and common mental disorders, less than 60% sought help.⁴¹ An oncology nurse-directed intervention consisting of regular in-person visits and phone calls was shown to improve depression and anxiety in patients newly diagnosed with cancer.⁴²

Methods to Improve Dosing Adherence

Interventions to Improve Dosing Adherence. Many research-backed methods have shown improvements in medication adherence (Table 5). One cost-effective strategy is the use of pillboxes to simplify complex medication regimens. A meta-analysis of packaging interventions (eg, pillboxes and blister packs) supported this by documenting increasing

medication adherence (71% for the treatment group vs 63% for the control).⁴³ However, not all drugs can be repackaged as many lack stability data when stored outside of the original packaging.⁴⁴ Automated interventions, such as daily messages and beeper reminders, have increased adherence by almost 20%.⁴⁵ Computerized reminders may be low-cost and scalable but could be challenging to implement in elderly patients who lack familiarity with new technologies.

Behavioral interventions may improve patients' mood symptoms, thereby increasing adherence. An integrated intervention of cognitive-behavioral therapy and medication monitoring was found to improve medication adherence and mood symptoms compared to medication monitoring alone,⁴⁶ indicating that behavioral interventions add value. Patients have also reported that trust and respect are paramount to building a patient-provider relationship that promotes medication adherence,⁴⁷ hence personalized contact with the health care team may be necessary.

Selection of Treatment to Minimize Poor Adherence.

Selecting a therapy that aligns with patient preferences may increase satisfaction, which is associated with better adherence and persistence.⁴⁸ Patients may prefer oral anticancer therapies because they are self-administered at home and do not require clinic visits (Table 6). Fear of needles, which is common and associated with health care avoidance, may also contribute to a preference for oral therapies.⁴⁹ Varying skin-to-muscle ratios and body mass index could complicate injection procedures and lead to bone/nerve injury and lack of efficacy.

On the other hand, oral therapies often require frequent, regular dosing (eg, daily or multiple times a day) and tend to have short half-lives that increase the risk of treatment failure if patients consistently fail to take their medicine as prescribed. Injections and drug implants are mainly administered by health care providers. They require a clinic visit, so direct patient contact allows monitoring of adherence and provides support (eg, calling with reminders to schedule appointments). A study found over twofold higher adherence rates (determined by the proportion of days with medication) in patients prescribed long-acting injections in comparison to oral medications ($P < .001$; Figure 2).⁵⁰ Sixteen percent more patients treated with oral drugs had at least 1 gap in therapy compared to those treated with long-acting injections (91% vs 75% of patients).⁵⁰ Clinicians should discuss therapy selection with their patients including factors such as the lowest nonadherence risk based on unique circumstances and preferences.

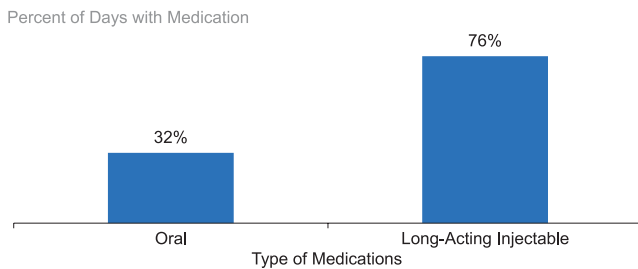


Figure 2. One-year medication adherence rate by types of medications.⁵⁰ Patients between 16 and 30 years old with a new diagnosis for a psychotic disorder were retrospectively evaluated during a 12-month duration. Adherence was defined as the proportion of days with medication. Patient-specific long-acting injectable dosing frequencies were used to calculate the proportion of days covered.

Impact of Oral Anticancer Therapies on Treatment Monitoring

There are some challenges to treatment monitoring for patients on oral anticancer therapies. First, there are no accurate or practical methods of tracking adherence to oral medications, which means that clinicians will not be able to accurately evaluate ongoing adherence and intervene if patients are not taking their medication correctly. Second, routine laboratory tests such as PSA and T levels to monitor disease progression and hormone suppression for patients receiving oral medications may be performed less frequently since patients are not required to visit the clinic as they would with regular periodic injections. Additionally, AEs related to androgen receptor axis-targeted therapies (eg, hypokalemia or hypertension) may not be treated in a timely manner without regular clinical visits. The AEs negatively

impact the patient's QoL and, in extreme cases, may lead to treatment discontinuation. Given the challenges of tracking oral medication adherence and monitoring patients who do not regularly visit clinics, oral anticancer therapies may be appropriate for patients who are likely to be consistently adherent to the dosing regimen. Still, ongoing clinic attendance remains necessary for disease monitoring.

CONCLUSIONS

Dosing adherence is essential for optimal treatment efficacy. However, there are many barriers to adherence that clinicians should be aware of when prescribing medications. Simplification of dosing is the intervention with the most substantial positive effect on adherence.¹⁸ Patient education and follow-up by a medical team member may identify specific patient issues and thereby increase adherence. Long-acting injections and oral medications have different benefits and drawbacks. For example, long-acting injections offer less frequent dosing schedules, and lower medication management burdens but require regular travel to clinics. AEs cannot be avoided following dosing. Oral medications can be conveniently delivered to the patient's doorstep and avoid needle sticks but require greater patient responsibility for continuous dosing with more opportunities for nonadherence. Health care teams should assess adherence barriers for each drug and patient, allowing clinicians to tailor treatment accordingly to minimize nonadherence risk and avoid potential adverse clinical outcomes.

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