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INTERVENTIONS TO PROMOTE ADHERENCE WITH ORAL AGENTS

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Abstract

Objectives—The advent of oral therapies has dramatically changed the landscape of cancer therapy. Yet the degree to which patients actually take the prescribed agents as ordered remains unknown. This article outlines the challenges that oral chemotherapy agents present to both patients and providers and suggests interventions for promoting adherence.

Data Sources—Published articles and web resources.

Conclusion—Barriers and facilitators to medication adherence are reviewed and interventions to promote medication adherence are presented. Strategies that include patient education and symptom management can promote adherence.

Implications for Nursing Practice—Maximizing adherence to oral chemotherapy agents can have many positive outcomes, but most important is improvement in overall survival and life expectancy. Other outcomes include improved safety and quality of life. Patients risk improper dosing and an increase in disease recurrence when there is nonadherence with medications. Correct dosing, education, and symptom management are all critical to ensuring adherence. Nursing interventions that incorporate education, early symptom identification, and reminder prompts can improve outcomes.

Keywords

Cancer; oral chemotherapy; adherence; symptom management; interventions

The advent of oral therapies has dramatically changed the landscape of cancer therapy. Oral agents were first introduced in the 1940 to 1950s,^{1,2} and following the discovery of signaling pathways that regulate cellular activity, their development rapidly increased.² With their development, the delivery of chemotherapy has changed from an inpatient to an outpatient model and now is yet again in transition as many oral therapies are managed in the patient's home environment. Yet the degree to which patients actually take the

prescribed agents as ordered remains unknown. Efficacy reports on newer oral agents are based on studies that may not have taken adherence rates into account, although adherence rates impact dosing, adverse events, and, ultimately, overall survival.

Oral cancer therapies have several advantages, including greater flexibility and convenience for the patient and minimal disruption of activities of daily living. In one study of 103 patients, 89% reported a preference for oral chemotherapy over infusional therapy,³ noting that oral chemotherapy did not require intravenous access or additional visits to the clinic/hospital for treatment. Yet oral cancer therapies present a variety of challenges to patients, health care providers, and health care institutions. Some of these challenges were examined in two recent studies. The first study, by Weingart et al,⁴ examines the issues related to institutional safety practices with oral chemotherapy and found that 50% of the centers surveyed had no safeguards for prescription writing, and only one third provided special training or certification for those who educated patients about oral chemotherapy agents. In a study of adherence, Barron and colleagues,⁵ looked at the early discontinuation of tamoxifen (Nolvadex; AstraZeneca Pharmaceuticals LP, Wilmington, DE). Although not a chemotherapy agent, tamoxifen, a hormonal agent, is prescribed for breast cancer treatment and it has associated side effects that may impact adherence. The researchers found that within 1 year and within 3.5 years of starting tamoxifen, 22.1% and 35.2% of patients, respectively, had discontinued therapy.⁵ In their mini-review of six studies, Escalada and Griffiths⁶ found high levels of compliance with oral chemotherapy, but the results varied because the studies used different methods of operationalizing and assessing adherence.

Adherence is defined by the International Society for Pharmacoeconomics and Outcome Research as “the degree or extent of conformity to the recommendations about day-to-day treatment by the provider with respect to the timing, dosage, and frequency.” and “the duration of time from the initiation to the medication to discontinuation of therapy.”⁷ Often the terms “compliance” and “adherence” are used interchangeably, but the latter is the preferred term. Issues with adherence have been addressed in patients with chronic asthma,⁸ depression,⁹ diabetes,¹⁰ hypertension,¹¹ HIV/AIDS,¹² and a variety of other diseases. However, while adherence issues are not new in health care, their importance is growing in cancer care as more oral agents are being developed and used to treat patients. Unfortunately, there is no gold standard for measuring adherence;^{6,13,14} this affects study design and methodology for nurse scientists, as well as pharmaceutical companies developing these novel agents. (See article on assessment and measure elsewhere in this issue.)

Factors Influencing Adherence

The World Health Organization proposes five types of factors that may impede adherence to therapies; they are patient-related, condition-related, therapy-related, social/economic-related, and health care team/system-related factors.¹⁵ Each of these is described next, as well as summarized in Table 1 in a coaching guide format that can be used during patient teaching.

Patient-Related and Condition-Related Factors

Patient-related and condition-related factors include cognitive impairment, comorbidities, gender, psychopathology, and other medications. Barron et al⁵ found that among women taking tamoxifen, young age (35 to 44 years) and old age (over 75 years), the number of prescription medications, and psychological problems contributed to adherence problems. Female gender has also been shown to have an impact on adherence and self-care in diabetes¹⁶ and in cardiac rehabilitation,¹⁷ with female participants in both studies demonstrating poorer outcomes. Briesacher et al¹⁸ reported a review of cost-related

nonadherence (CRN) across many diagnoses. CRN was associated with not having prescription drug coverage, medical costs, and heavy disease burden.¹⁸ Finally, DiMatteo et al¹⁹ found that nonadherence was 27% higher in patients who were experiencing depression. Careful assessment of patient-specific factors is important when developing strategies for adherence. Being aware of factors such as depression or co-morbidities can help the nurse to tailor interventions specific to individual needs.

Therapy-Related Factors

Therapy-related factors include adverse events, length of treatment, patterns of dosing, polypharmacy, and route of administration. For cancer patients, these factors are illustrated in the complexity of the regimen, the need for safety precautions, getting prescriptions refilled, and occurrence of side effects.

Complex regimens—Complex regimens increase the risk of nonadherence. Patients who are on multiple medications, either for cancer treatment or who have co-morbid conditions, have to navigate the complexity of integrating a new chemotherapy agent into their lifestyle and current medication regimen, which can pose additional risks of medication and/or food interactions. For example, a woman with advanced or metastatic breast cancer whose tumors overexpress HER2 may receive treatment with lapatinib (Tykerb; GlaxoSmithKline, Middlesex, UK) and capecitabine (Xeloda; Roche, Basel, Switzerland), she needs to take the lapatinib once a day, 1 hour before a meal or 1 hour after a meal, while the capecitabine should be taken twice daily, with food or within 30 minutes after eating. One way to assist patients with complex regimens is to use a spread sheet approach, where medication dosages and times are listed for each day. Individuals can then check off the sheet after a medication is taken. Some medication distribution companies are preparing medications in individualized blister packs, which provide a full week's supply of medications in labeled "pop open blisters" for each prescribed dose within a given day.

Safety and handling—Chemotherapy is hazardous, whether in intravenous or oral form. Safe handling of oral chemotherapy is essential in protecting patients, caregivers, and the environment. According to Griffin,²⁰ the risk of exposure is not diminished just because the medications are administered outside the health care setting. Patients and family members should be taught to protect their skin from the pills by wearing gloves or washing their hands immediately after handling if gloves are not available. It is also important to instruct patients to not crush or open pill capsules because of the risk of inhalation of dust particles from the medication.²⁰ Patients should be instructed to return any unused medications to the oncology clinic for disposal.

Prescription refills—In a survey conducted by The Wall Street Journal and Harris Interactive,²¹ 27% of patients did not get their prescription refilled as recommended by their doctor. Though the reasons were not stated, one patient said during a recent informal focus group at our institution, "If I only understood how important the medicine (oral chemotherapy) was to take, I might have done better. I understood the IV part, but my disease has progressed and I am now on a new therapy. I cannot help wondering sometimes if by missing or skipping doses, my disease progressed."

Initial prescriptions and refills of prescriptions may pose challenges to patients whose local pharmacy does not carry some of the agents used and cannot provide patient education and counseling. Adherence to treatment is also impacted by pharmacist time constraints and patients' refusal of medication counseling. In a study of repeat cancer prescriptions for ambulatory patients, 56% of the patients had satisfactory refill adherence, 30% had an oversupply, and 14% had an undersupply.²² In a study of chronic disease patients who

received a pharmacist-delivered telephone intervention 2 weeks after starting a new medicine, researchers found nonadherence and medication-related problems to be significantly lower in the intervention group ($P = .032$, $P = .021$, respectively) than in the control.²³

Side effects—Adverse events, side effects, and dosing schedules are the focus of patient counseling and education when oral chemotherapy is prescribed. Symptoms associated with oral agents can be just as distressing to the patient as infusional agents. Dermatitis acniform, gastrointestinal irritation, and palmar-plantar erythrodysesthesia are symptoms commonly associated with oral agents and impact not only adherence rates, but body image and quality of life. Patient awareness of side effects, dose adjustments by the healthcare provider, and adaptation of the therapy into patients' lifestyles are critical. Nursing interventions that facilitate symptom management have been associated with increased adherence to oral chemotherapy agents.²⁴ Educational strategies each have advantages and disadvantages and should be tailored to meet the patient's needs.²

Socioeconomic-Related Factors

Socioeconomic-related factors include attitude toward treatment, cost of treatment, financial support, distance to treatment center, social rank of illness, social support, and supervision of treatment. DiMatteo²⁵ found that the odds of patient adherence were 3.60 times greater in patients receiving practical social support, 3.03 times greater in patients with close and cohesive families, and 1.53 times lower in patients who had conflict in their families. Being married or living with another person increased adherence modestly.²⁵

Patient understanding of disease and treatment affects their attitude toward adherence.²⁶ Patients who have received prior infusion therapy or who are receiving it in combination with oral therapy need to recognize the importance of taking their oral treatment on time to maximize the effects on outcomes. Financial impact, in particular out-of-pocket costs, and travel to a facility for care affect adherence to a degree that is often overlooked by health care providers. Lost wages, gas, parking, childcare costs, and fixed incomes can also impact adherence.^{27,28} In a study of 1,088 Medicare attendees, 32% reported CRN, 24% skipped doses because of cost, and 13% did not fill their prescription.²⁹ Patients may have high copayments depending on their health insurance plans, and patients on fixed incomes may not be able to afford the additional expense. In their study of 51 patients, Lebovits et al³⁰ found that patients with lower socioeconomic status had higher rates of nonadherence. Patients whose barrier to adherence is cost related can be referred to a social worker or to the pharmaceutical company's patient assistance program.

Clinician-Related Factors

Finally, clinician-related factors include aftercare management, belief in the treatment, the doctor/patient relationship, the use of guidelines, and provision of information. There are many challenges with oral therapies. Providers face issues regarding safety practices that include safe handling, prescription frequency, and education of clinicians and patients.

For many oncology patients, long-term follow-up is the standard of care because of the chronicity of the disease, the need for surveillance, and the late effects of treatments. However, a survey of primary care providers found that they were uncertain about the required surveillance, and only 52% were comfortable taking responsibility for surveillance of cancer recurrence.³¹ Research on patient/provider relationships indicated a need for good communication and patient participation in the treatment.^{32,33} System issues such as polypharmacy, combined treatment modalities, and lack of communication between providers can result in lack of adherence. For example, a patient told to initiate an aromatase

inhibitor following radiation therapy may require a telephone reminder several weeks later, when it is time to start her medication. As patients become better consumers and advocates of care, health care providers need to be aware of how their behaviors and communication patterns affect patient adherence. Provision of information is the cornerstone of patient empowerment. Educational as well as behavioral strategies need to be incorporated into the treatment plan.³⁴ Nursing interventions have been shown to have a positive impact on adherence as well as symptom management.³⁵⁻³⁸ However, because of lifestyle variations not all interventions work with all patients.

The frequency in which to prescribe oral chemotherapy agents is another issue that providers must face. Some manufacturing companies will dictate how often certain medications can be dispensed. Thalidomide and lenalidomide prescriptions can only be written for 28 days, and refills are not allowed on thalidomide.³⁹ This allows for better monitoring, control over medications, and ultimately improved safety when patients are required to return for refills. A multidisciplinary group at Dartmouth-Hitchcock Medical Center (Lebanon, NH) designed a program to help monitor patients on oral chemotherapy agents in the home. The program involved an oncology certified nurse calling patients on oral chemotherapy and verifying the medication, dose, frequency, and duration with the actual written prescription.⁴⁰ Their research found that many patients were not taking the correct dose or were taking the medication longer than intended. Thus, they recommended that physicians prescribe enough medication for only one cycle of chemotherapy at a time to prevent these potential problems.⁴⁰

According to the safety standards written by the American Society of Clinical Oncology and the Oncology Nursing Society, it is recommended that oral chemotherapy agents be written with a time limitation to allow for appropriate evaluation of the patient. However, specific time frames are not identified.⁴¹ Requiring patients to return for clinic visits or participate in telephone evaluation at regular intervals is a strategy for adherence. During these clinician interactions, providers can assess for barriers to adherence, help to manage medication side effects, and suggest cues to help patients remember medications.⁴²

Strategies for Adherence

Supervision of oral therapies may entail a variety of approaches, and these approaches often have associated costs. Many of the following methods such as pill boxes and blister packs can alleviate some of the confusion. There are several reminder triggers that can be utilized to improve patient adherence to their oral therapies. For many of these interventions there is limited evidence regarding their effectiveness. The following section is a review of possible strategies to promote adherence.

Reminder Triggers

The use of pill diaries has been found to be an effective method in conjunction with other methods to improve medication adherence. In a pilot study by Lee et al,⁴³ medication diaries were used in combination of medication electronic monitoring system (MEMS) and pill counts.⁴³ Participants recorded the time and date of each dose and then the diary was reviewed by clinical staff. This enhanced understanding and adherence with the prescription.⁴³ However, according to a study by Mayer et al,⁴⁴ pill diaries may overestimate adherence rates. Self-reporting of data adherence may be higher because patients give the numbers that the observer wants to see.

Pill boxes can be helpful to patients in organizing their pills by day and can provide visual cues as to whether they took the days' medication. In a study of 25 patients, patients

preferred the use of the daily pill boxes over conventional pill bottles, but no significant improvement in adherence was found in the group using the pill boxes.⁴⁵

With the complexity of so many chemotherapy regimens, patient calendars or spreadsheets can also be useful in helping patients stay on track with their pill schedule. Calendars or checklists can be used as a reminder to order medication and to help individuals anticipate the need to make sure they have an adequate supply of medications before travel or vacations.^{24,46} Similarly, postcard reminders are another strategy used by specialty pharmacies to remind individuals to refill medications on time. Specialty pharmacies often use interventions such as calendars, diaries, and dosing sheets to promote timely refills and ultimately improve adherence and patient outcomes.⁴⁷

Blister packs have been shown to improve understanding of complex regimens and in turn, enhance medication adherence.⁴⁸ This form of packaging allows individuals to access one dose of medication at a specific time labeled on the package. Patients can easily see whether or not they have taken a dose at the prescribed time. One barrier to this method is the increased cost related to these packs. Also, not all medications are available in blister packs.

Cellular phones/alarms—Cellular phones are a popular method to help remind people to take their pills. The alarm can be set to go off at the time the medication is to be taken. There is also message texting available to be used as a reminder. In a study by Miloh et al,⁴⁹ texting was used as a reminder system for immunosuppressive therapy in pediatric post liver transplant patients. The findings were improved adherence and a reduction in rejection episodes. The median age of participants in the study was 15 years. The results of this study can not necessarily be generalized to the oncology setting, but with the increased use of cell phones by so many in the population, this could be an effective intervention to try. In a current study, Openshaw⁵⁰ is investigating the use of cellular phones in long-distance management of cancer pain. The study will evaluate feasibility of using cellular phones to assess the effectiveness of long- and short-acting opiates for management of pain from metastatic cancer.

Some patients report using alarm clocks or kitchen timers to help them remember to take their medication. Patients who take their medications with food can use the timer or the stove or microwave clock to prompt them to take their medications. Others use timers on televisions. One individual remembers to take her daily medication with the noon news.

Electronic pill bottles—A pilot study funded by the US Department of Health and Human Services is currently under way to evaluate the effectiveness of talking pill boxes and improving medication adherence in those with low functional health literacy.⁵¹ Medication instructions are recorded for the patient to replay as needed to promote understanding. Application of the talking pill box intervention could be applied to the oncology setting to assist patients with complex drug regimens; however, there is no evidence regarding effectiveness in this population. This intervention would not assist patients in remembering to take their medications, only in understanding the directions for use. Results of this study will be forthcoming.

Medication electronic monitoring system (MEMS) bottle caps contain a microchip that records date and time when opened.⁵² MEMS have the ability to detect when an individual has neglected to take a medication or when they have taken more medication than prescribed. Several researchers have used these devices to measure adherence, but acknowledge limitations. These devices are expensive and impractical.⁵³ Further, the MEMS caps only show when the bottle was opened, not whether the patient actually took a prescribed dose. In a study by Simons et al,⁵⁴ the authors noted that the MEMS may have

influenced the positive adherence rate in a control group by producing altered behaviors because patients were aware of being observed (Hawthorne effect).⁵⁴ MEMS have the potential to detect when patients have taken too much medication. A newer device, the MEMS Smart Cap, includes an electronic reminder beeper and an indicator that shows how many hours have elapsed since the bottle was opened.⁵² Use of MEMS limits the ability to use other memory trigger systems, such as daily pill box dispensers that can coordinate all of an individual's medication for the entire day or week. The major weakness of MEMS is that the link between opening the bottle and taking the correct dose is implied.

Newer technology, such as a computerized pillbox for home use, can also be used.⁵⁵ This device can manage up to a month's worth of 10 drugs and alerts the patient when a dose should be taken. A barrier to this device is cost, and it may not be convenient for patients who are working or traveling to carry around an entire month's supply of medication. Improving medication adherence could be accomplished through the use of many of the methods discussed; however, the literature is lacking in support of these methods.

Provider Support and Surveillance

The Multinational Association for Supportive Care in Cancer (MASCC) identified that education is essential to ensure that oral agents are being taken correctly. This group has developed and evaluated a teaching tool for patients receiving oral agents for cancer treatment. The tool was created by a panel of experts, reviewed by an oncology pharmacist, and then evaluated in 15 countries. The MASCC Teaching Tool for Patients Receiving Oral Agents for Cancer (MOATT) is available free of charge on the MASCC web site (www.mascc.org). The tool that helps clinicians identify barriers and facilitators to adherence also provides suggestions for patient education. Tips such as teaching patients to plan ahead for travel and weekends, as well as suggestions for reminder cues, such as timers and calendars, are included. The instrument, which is available in several languages, provides a structured format to ensure that assessment, symptom management, and strategies for adherence are addressed.

Symptom Management

The Health Belief Model can be used to enhance understanding of patient motivation and to increase compliance among patients using oral therapies.² Based on concepts in this model, Moore² advocates for patient/family education and side-effect management as key strategies to promote adherence. Side effects of oral agents are similar to intravenous agents, and yet new side effects, such as skin rashes, also occur. Most side effects can be managed with current symptom management strategies, but the best practice for skin rashes has yet to be established, but guidelines do exist.

Nurses need to be an essential part of the patient team for providing patient teaching and management of side effects related to oral chemotherapy treatment, just as they currently are with intravenous treatments. All patients need to know how to monitor for expected side effects and how to call for health care support because symptoms can quickly escalate in the home setting.⁵⁶ Patients may decrease or skip doses if the side effects are too troubling; as a result, patients may not receive the recommended dose. Individualized coaching provided by nurses can help with side-effect management and provide strategies to help patients remember to take medications as prescribed.

Some studies have explored the influence of provider support and coaching interventions on oral chemotherapy adherence.^{23,24} These projects have several things in common: individualized approaches, patient education, symptom management focus, and involvement of a health care professional. Decker et al²⁴ completed a pilot study that explored the use of

an automated voice response (AVR) system to monitor adherence to oral chemotherapy medications.²⁴ Thirty ambulatory oncology patients who were treated at two cancer centers received a symptom management tool kit that they used in conjunction with weekly AVR calls. These calls assessed adherence to oral agents and the severity of 15 symptoms. Patients who reported a symptom severity of >4 (on a scale of 0 to 10) or who had adherence rates below 100% were called by a nurse for assistance. Results indicated a 23.3% nonadherence rate to oral chemotherapy medications because symptoms and forgetting to take the medication. An association between symptom management and adherence was found.²⁴

A currently funded National Cancer Institute trial by Schneider and colleagues⁵⁷ will measure adherence rates in 100 individuals started on an oral chemotherapeutic agent. The control group will receive standard chemotherapy education, “whereas participants in the experimental group work with an advanced-practice nurse who will assess their individual needs and follow up with telephone reminders and coaching.”

Conclusion

“Drugs don’t work if people don’t take them.” C. Everett Koop (Former US Surgeon General).

Maximizing adherence to oral chemotherapy agents can have many positive outcomes, but most important is improvement in overall survival and life expectancy. Other outcomes include improved safety and quality of life. Patients risk improper dosing and an increase in disease recurrence when there is nonadherence with medications. Further, health care costs are decreased when a medication is taken as ordered, but they are increased when the dose is increased by a patient who thinks “more is better.” Correct dosing, education, and symptom management are all critical to ensuring adherence. Nursing interventions that incorporate education, early symptom identification, and reminder prompts can improve outcomes.

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TABLE 1

Coaching Guide for Medication Adherence

	Date Suggested	Effective (Y/N) Notes
Assess Factors that Influence Adherence		
Patient-related factors		
Therapy-related factors		
<ul style="list-style-type: none"> • Complex regimen <ul style="list-style-type: none"> - Understanding of medication pharmacology (Missing doses decreases efficacy) - Understanding medications schedule (time of day to take medicine, take with/without food; medication calendar) • Fear of safe handling <ul style="list-style-type: none"> - Advantages and responsibilities of oral chemotherapy agents - Safe Handling (wear gloves, don't crush pills) • Refill issues <ul style="list-style-type: none"> - Rationale for adherence. (In order to evaluate if this drug works for your cancer, you need to take it as prescribed). • Side effects <ul style="list-style-type: none"> - Side effect management strategies - Profile sheets for each medication with side effects and management strategies - 1) Side effect management sheet for _____ - 2) Side effect management sheet for _____ - 3) Side effect management sheet for _____ - Other: • Social/economic factors • Other 		
Clinical-related factors		
<ul style="list-style-type: none"> • Communication issues among providers • Other 		
Behavioral/Reminder Strategies		
Medication reminder box (alarmed Y/N)		
Event reminders (ie, take medications together, take with meals)		
Set up medications daily/weekly/plans for travel		
Have caregiver remind you to take medication		
Medication calendar with check offs		
Alarm systems (kitchen timer, bedside alarm)		
Phone alarms		
Other:		
Provider Support and Surveillance Strategies		
Nurse phone calls weekly		
Have caregiver double check medication box		
Congratulations with refill		

	Date Suggested	Effective (Y/N) Notes
Refill reminder post card Notify caregiver of patient concerns, ask provider to reinforce <ul style="list-style-type: none">• Medication schedule ____• Rationale for medication ____ Phone call to support person Referral to counselor Referral to support group Referral to patient assistance program (financial support) Other:		