Adherence is a potentially significant issue in oral therapy for breast cancer. Suboptimal adherence to medication regimens impacts clinical benefit and can result in treatment resistance, disease progression, and even death. Nonadherence is a greater issue with oral medications because the majority of responsibility shifts from healthcare professionals to the patient. Improving adherence to medication regimens can impact patients’ likelihood of successful clinical outcomes. Many factors contribute to adherence behavior, such as complex dosing or administration requirements, cost, and a lack of understanding of the importance of adherence. Most of the factors are controlled by the patient, but nurses can play a significant role by monitoring patients, identifying potential barriers to adherence, and implementing intervention strategies. If barriers to adherence with oral therapies cannot be overcome, the use of IV therapies with equivalent efficacy and acceptable safety should be considered. Using IV medication, when available, can improve outcomes by ensuring that the patient receives the correct and optimal dose of medication at every cycle.

Patients are considered to be nonadherent if they miss doses of medication, take additional doses to those prescribed, or take doses either in the wrong quantity or at the wrong time (Ruddy, Mayer, & Partridge, 2009). This is distinguished from persistence, which refers to taking the medication regimen for the length of time prescribed by the provider (Ruddy et al., 2009). The World Health Organization (2003) stated that, on a worldwide basis, only about 50% of patients typically take their medicines as prescribed. Nonadherence causes 125,000 deaths annually in the United States and leads to 10%–23% of hospital and nursing home admissions (Merck Manual of Medical Information, 2008). Medication nonadherence also impacts the overall healthcare system heavily. Total direct and indirect healthcare costs related to nonadherence have been estimated at $177 billion annually (Ernst & Grizzle, 2001). The full benefit of an effective medication is only achieved if patients follow their prescribed regimen. This article discusses challenges that impact adherence to breast cancer therapies and recommendations to improve it.

Nonadherence to Treatment Among Patients With Breast Cancer

Although generally believed that nonadherence to therapy regimens would be less pronounced among patients with cancer because they tend to be highly motivated (Weingart et al., 2008), the medical literature indicates that nonadherence to oral treatment regimens remains an obstacle for many patients with cancer (Ruddy et al., 2009; Weingart et al., 2008). Among studies of patients with breast cancer, the rate of adherence to treatment regimens varies greatly, from 53% (Lebovits et al., 1990) to 93% (Thompson, Dewar, Fahey, & McCowan, 2007). This wide range can be attributed to a number of factors, including characteristics of the study (e.g., time horizon) and type of regimen (e.g., pill burden). For patients with breast cancer, the availability and use of orally administered prescription therapies are increasing, making an understanding of what factors impact patient adherence increasingly important. In addition, some patients prefer oral medications because they perceive them to be more convenient.

**At a Glance**

- Suboptimal adherence to oral medication regimens impacts clinical benefit and can result in treatment resistance, disease progression, and death.
- Nurses, in collaboration with other healthcare professionals, play an important role in monitoring adherence by identifying potential barriers and implementing intervention strategies that would help to enhance adherence and, therefore, improve clinical outcomes.
- If barriers to adherence with oral therapies persist, adherence and the optimal dose of medication can be consistently ensured with IV therapy, if available.
and less toxic than IV agents. This belief also may contribute to the increased use of oral agents and underlines the need for patient education around medication adherence.

IV therapies are administered under the supervision of a healthcare professional in a controlled setting and adherence is consistently ensured when patients attend their scheduled appointments. With oral medications, however, nonadherence is a greater issue because the responsibility for adherence shifts to the patient. The implications of nonadherence to oral breast cancer therapies are serious. Poor adherence to tamoxifen, for example, has been significantly associated with increased risk of death from breast cancer (Thompson et al., 2007). Osterberg and Blaschke (2005) stated that the ability for a provider to recognize nonadherence is poor; mixed results have been reported for interventions to improve adherence. Nurses may help to identify and solve issues relating to adherence. For example, a nurse may uncover a patient’s misunderstandings or concerns and could help alleviate them.

Factors Impacting Adherence

Most of the factors that impact adherence to medications are controlled by the patient. When assessing patient adherence to orally administered breast cancer therapies, nurses should proactively evaluate dosing and administration requirements, multiple concurrent therapies, adverse effects, condition-related challenges, age, psychological factors, education, physical limitations, and cost of medications.

Dosing and Administration Requirements

Treatment schedules that call for two or more daily doses are associated with lower adherence than those with once-daily dosing (Claxton, Cramer, & Pierce, 2001). With oral medications, patients may potentially self-modulate their doses. For example, patients might increase their dose if they think the therapy is not working or decrease their dose if they think therapy is too toxic. Some medications are more effective or tolerable when taken with or without food. If patients do not take their medications as directed, this may result in a lack of efficacy or an increase in side effects that may have a significant effect on adherence.

Patients also may be prescribed a complex daily regimen, consisting of more than one oral medication with complicated dosing and administration requirements. This could exacerbate poor adherence to therapy as there also would be an increased likelihood of patients missing a dose or taking it at the wrong time. Some oral-only regimens used in breast cancer are complex and have a high total pill burden. Drugs in a combination regimen may need to be taken at different times, with or without food.

Multiple Concurrent Therapies

Patients on multiple medication regimens are faced with additional dosing and administration challenges. These challenges are greater for multiple chronic conditions. For example, among patients with breast cancer who were prescribed a five-year course of tamoxifen, patients who had another prescription added were more likely to discontinue tamoxifen therapy than those who did not (Lash, Fox, Westrup, Fink, & Silliman, 2006). A study by Kennedy, Tuleu, and Mackay (2008) was designed to establish the rate of failure to fill prescriptions among Medicare patients. This study found that a direct, linear relationship exists between the number of chronic comorbidities and the rate of failure to refill at least one prescription. Interestingly, the overall self-reported rate of failure was low, at 4.6% (664 of 14,464 patients).

In addition to multiple prescribed regimens, many patients may regularly take one or more over-the-counter medications or supplements, which may further exacerbate nonadherence. Drug-drug interactions also are an issue with many contraindications because drugs often are metabolized by the same pathway (e.g., cytochrome P450 enzyme [CYP3A4]). For example, lapatinib has warnings about concomitant treatment with inhibitors and inducers of CYP3A4 and altered gastric pH (GlaxoSmithKline, 2008). Drug-drug interactions with other oncology drugs and drug therapies required for comorbid conditions are of great importance because they are a major cause of morbidity and mortality. The exact number of deaths related to drug interactions is unclear and has been estimated to range from an annual incidence of 7,000 (Committee on Quality of Healthcare in America, 2000) to more than 100,000 (Lazarou, Pomeranz, & Corey, 1998).

Adverse Effects

Older adult patients are less likely to adhere to an intervention that is associated with a high incidence of adverse events (MacLaughlin et al., 2005). A study by Lash et al. (2006) found that adverse effects had a substantial influence over whether patients with breast cancer adhered to their tamoxifen therapy. This is particularly true for patients who do not feel that the relief they gain from their symptoms is equivalent to the benefits of treatment or for patients who do not consider their therapy to be beneficial (Lash et al., 2006).

Nonadherence can worsen adverse effects or cause new ones, such as withdrawal symptoms (MacLaughlin et al., 2005). Complete adherence might render the therapy ineffective because many drugs function within a narrow therapeutic range. Drug absorption also may be reduced in patients who vomit within a short time after taking a dose. Ultimately, this ineffectiveness may usher in a cycle of poor adherence if the patient begins to feel that the underlying condition is worsening despite treatment (MacLaughlin et al., 2005). Adverse effects also influence activities of daily living and appearance, which the patient might consider to be more important than treating their disease. Poor management of side effects also may contribute to patient nonadherence. Side effects, such as diarrhea and stomatitis, may interfere with oral drug therapy (Moore, 2005). Because treatment interruption or dose modification to manage adverse effects affects dosing of many treatments, healthcare providers should work as a team to proactively manage adverse effects and to ensure that the patient is prepared for their potential onset. Dose interruption or modification could quickly control side effects and prevent worsening of symptoms (Moore, 2005; Moore, S.H., 2007). In addition, patients should be informed about what to expect when they begin therapy and whether any steps can be taken to relieve their side effects.

Condition-Related Challenges

For asymptomatic conditions, patients may be less likely to adhere to or persist with treatment if they do not experience a perceptible benefit from the medication or if they do not feel they
are sick. Adherence also may differ between patients based on their disease stage. Patients with early breast cancer may not feel as sick as those with metastatic breast cancer; consequently they may be less adherent to their medication regimen.

When patients are prescribed preventive rather than curative medications, “buying in” to the value of these types of therapies is essential. Adherence to tamoxifen therapy for the prevention of breast cancer recurrence is important because treatment with a five-year regimen has been shown to decrease the risk for metastases and death by 41% and 34%, respectively (Early Breast Cancer Trialists’ Collaborative Group, 2005). Rates of adherence to tamoxifen in patients with breast cancer have been assessed in a number of studies. Adherence rates vary from 45%–98% (Atkins & Fallowfield, 2006; Barron, Connolly, Bennett, Feely, & Kennedy, 2007; Grunfeld, Hunter, Sikka, & Mittal, 2005; Lash et al., 2006; Murthy, Bharia, & Sarin, 2002; Thompson et al., 2007; Waterhouse, Calzone, Mele, & Brenner, 1993) although, in the majority of the studies, the rate was greater than 75%. In addition, mean adherence during early endocrine therapy appears high but tends to decrease each year (Barron et al., 2007; Partridge et al., 2008).

Age

Multiple studies have shown that older adult patients are less likely to take medication correctly than younger patients (MacLaughlin et al., 2005; Murray et al., 2004). Adherence rates in patients older than age 60 are low (26%–59%) (LaFleur & Oderda, 2004; van Eijken, Tsang, Wensing, de Smet, & Grol, 2003) and nonadherence continues to be a major cause of hospitalization. Several studies have found that up to 26% of hospitalization among patients older than age 75 is caused by medication nonadherence (Chan, Nicklason, & Vial, 2001).

One of the reasons that older adults experience increased nonadherence rates may be multiple age-related chronic conditions that require complex medication schedules, including daily administrations of five to eight drugs on average (Chia, Schlenk, & Dunbar-Jacob, 2006). Adherence in this population also is more likely to be hindered by cognitive challenges, such as decreased memory or coping skills; physical challenges, such as impaired hearing and/or vision; and generation-specific perceived barriers to taking medication (Chia et al., 2006; MacLaughlin et al., 2005; Murray et al., 2004). Additionally, many older adult patients have a fixed income or rely on Medicare for pharmaceutical coverage; economic limitations are a commonly cited reason for nonadherence among this population (Kennedy et al., 2008; MacLaughlin et al., 2005).

Psychological Factors

Disorders with declining comprehension or memory loss are associated with adherence challenges (MacLaughlin et al., 2005). Among a subgroup of Medicare beneficiaries who self-reported a range of chronic conditions, those with a psychiatric condition were most likely to let a prescription go unfilled (Kennedy et al., 2008).

Patients who have a high level of control over their health and those who are confident in their ability to self-administer medication or manage adverse effects are likely to adhere to their prescribed regimens (Chia et al., 2006). However, some patients perceive oral medications to be less important and/or less “powerful” than IV therapy and, therefore, believe that they are unable to provide maximum clinical benefit. For example, patients may think that an oral medication strong enough to fight cancer should also have other adverse effects on the body (i.e., may hurt stomach). Other patients do not want oral medications because they do not want to assume full responsibility for medicating themselves, thereby potentially impeding their therapy. These concerns can lead to patients speculating scenarios, such as “what would happen if I forget to take my medication?” and “what if I have already taken it and then I take it again on the same day?”

Education

Instructions that accompany medications and are written for patients often are wordy and confusing to a general audience (Murray et al., 2004). Even within patient groups, an individual’s tendency toward adherence is influenced by his or her particular background (Morris & Schulz, 1993). The extent to which a patient can read, understand, and carry out health recommendations plays a role in how well a patient will follow a prescribed regimen. More information can be found on pages 18–20 of American Society on Aging and American Society of Consultant Pharmacists Foundation (2006).

Physical Limitations

Declining eyesight may limit a patient’s ability to read and interpret labels and dosing instructions. In these cases, larger print on labels and instruction sheets, accompanied by a verbal reinforcement of dosing instructions from the nurse, can remove this roadblock to correct administration (Murray et al., 2004). Conditions associated with manual weakness (e.g., arthritis) or peripheral neuropathy may affect how well a patient can remove a tamper-proof seal or open a pill bottle (MacLaughlin et al., 2005). Generalized physical weakness or ambulatory difficulties also may hinder patients in filling prescriptions or attending medical visits. In addition, having a physical disability positively correlates with cost-related barriers to adherence (Kennedy et al., 2008). If this issue is anticipated, the pharmacy can dispense the medication in a senior-friendly pill bottle. Dysphagia also impacts adherence from compromised ability to swallow. Further compounding these barriers to adherence, patients may mask any physical limitations that may interfere with adherence.

All of these factors have been suggested to be causes of the observed lower adherence rates in patients with glaucoma, chronic obstructive pulmonary disease, or breast cancer being treated with tamoxifen (MacLaughlin et al., 2005).

Cost of Medications

The high cost of medications may be a barrier to medication use. In a study of almost 14,000 Medicare enrollees, 29% of people with disabilities and 13% of seniors reported skipping doses or not filling a prescription because of cost (Soumerai et al., 2006). Data also have attributed the elevated cost of medications to the high and persistent nonadherence over time (Madden et al., 2008). Medicare recipients most frequently cite drug costs (56%) and inadequate insurance coverage (20%) as reasons for not filling a prescription (Kennedy et al., 2008). Limited access to healthcare services, lack of financial resources, and
burdensome work schedules also are associated with poor adherence to medication regimens (Osterberg & Blaschke, 2005). A report jointly published by the Kaiser Family Foundation and the American Cancer Society (Schwartz, Claxton, Martin, & Schmidt, 2009) addresses financial concerns of people with cancer related to the current health insurance system in the United States.

**Methods to Assess Adherence**

Well-controlled trials have not identified an adherence monitoring method that is superior to others. In a review of adherence to medications in older adult patients, MacLaughlin et al. (2005) found that several methods for assessing adherence are available, including self-reporting, reviewing prescription refill records, pill counting, and using medication management assessment tools. The authors concluded, however, that these methods are unreliable and inaccurate and that additional research is still required to optimize adherence in this patient population.

Direct measurements used to assess adherence include conducting biologic assays to measure plasma levels of a drug or its metabolites, an accurate and objective method of assessing adherence. However, many treatments have such short plasma half-lives that measuring the blood plasma level would only identify whether patients had taken their most recent dose. In addition, conducting these assays is time-consuming and expensive, and patients may consider it intrusive.

Indirect measurements of adherence include self-reporting, reports from family members and healthcare providers, prescription fills, pill counts, and electronic monitoring. Self-reporting is a practical and convenient method of measuring adherence. However, self-reporting has clear potential for patients to under-report nonadherence (Miaskowski, Shockney, & Chlebowski, 2008). Similarly, collateral reports from family members and healthcare providers tend to overestimate a patient’s ability to adhere to a medication regimen and adherence level (MacLaughlin et al., 2005; Paterson, Swindells, & Mohr, 2000). The Medication Events Monitoring System* (MEMS) study on adherence to therapy in patients with HIV infection demonstrated that physicians miscalculated adherence in 41% of patients and nurses misjudged adherence in 30% of patients (Paterson et al., 2000). Prescription fills and pill counts also tend to overestimate adherence (MacLaughlin et al., 2005) and could be undermined if patients remove pills or take more than one dose at a time (Osterberg & Blaschke, 2005).

An electronic monitoring system, such as MEMS, uses a computer chip that electronically tracks the times and frequency at which the bottle is opened. These devices are relatively expensive to implement but yield data that is precise and easily quantified (Kruk & Schwalbe, 2006). They also have been considered the most accurate way to monitor adherence (Kruk & Schwalbe, 2006) and are emerging as the “gold standard” for examining how patients self-dose (Lawrence, Allison, Chen, & Demand, 2008; Vrijens, Gross, & Urquhart, 2005). However, use of a MEMS device does not guarantee medication is actually taken and the price may not be affordable for individual patient use (MacLaughlin et al., 2005).

**Strategies to Improve Adherence**

A combination of two or more factors most often leads to medication nonadherence (MacLaughlin et al., 2005). These factors could be addressed by identifying patients who are unlikely to adhere to oral therapy. Management strategies, as well as key information that may improve adherence, are listed in Figures 1 and 2.

With oral medications, responsibility for daily adherence shifts to the patient. Taking oral medications at home reduces the amount of patient and healthcare professional interaction and patient-patient support that develops when patients regularly visit the office or infusion center. The health professional also has less opportunity to assess disease response and toxicity. Patients who receive oral chemotherapy may not receive the same level of education and monitoring as patients on IV chemotherapy (Moore, 2005).

A meta-analysis of 61 studies of interventions to improve medication adherence demonstrated a relatively low increase in adherence of 4%–11% (Peterson, Takiya, & Finley, 2003). The investigators also concluded that no single strategy appeared to work best. Kripalani, Yao, and Hanes (2007) published results from their systematic review of the literature on interventions to improve adherence. They assessed data from randomized, controlled trials of interventions published over a 37-year period (January 1967–September 2004) and reported that several types of interventions were found to improve medication adherence but very few significantly affected clinical outcomes.

Evidence reported by Fink, Gurwitz, Rakowski, Guadagnoli, and Silliman (2004) suggests that younger (younger than 45 years) and older (85 years or older) women, non-Caucasian women, patients who underwent a mastectomy, patients with estrogen receptor-negative tumors, and patients experiencing side effects are less likely to adhere to long-term oral breast cancer therapy. However, Fink et al. (2004) found that the factors previously observed to affect adherence (age, medication regimen complexity, and side effects) were not associated with tamoxifen discontinuance. The authors concluded that having four or more positive lymph nodes and patients’ perception of risks and benefits of tamoxifen therapy were critical for sustaining adherence.

- Patient and caregiver education
- Organizational methods (e.g., calendars, compartmentalized pill boxes, electronic reminder systems)
- Managing expectations and adverse effects in a proactive manner
- Telephone or e-mail follow-up by nurses, pharmacists, social workers, or corporate-sponsored programs
- “Easy-open” containers
- Large print on labels and instructional sheets
- Automatic dispensers
- Mail-order delivery or use of specialty pharmacy
- Consideration of IV therapy if appropriate

**Figure 1. Management Strategies to Promote Patient Adherence**

*Note.* Based on information from MacLaughlin et al., 2005.
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Patient Education and Communication

The ability of patients to adhere to prescribed regimens has received less attention than providers’ compliance with published guidelines. Heidenreich (2004) stated that causes for this include lack of awareness of the magnitude and scope of nonadherence, the view that adherence is solely the patient’s responsibility, and the lack of interventions to improve adherence.

In a self-reported survey posted on the Y-ME National Breast Cancer (now Breast Cancer Network of Strength) Web site, only 44% of respondents reported having education on the importance of taking oral medication as directed at every office visit (Kirk & Hudis, 2008). Likewise, a study of oncology nurses found that about 50% felt inadequately educated on oral chemotherapy agents and just 25% gave patients the necessary drug information (Kav et al., 2008). Patient management strategies to improve adherence are necessary to optimize efficacy and safety of oral therapies. Regular interaction with a healthcare provider may offset such risks associated with nonadherence. Patient adherence has been found to typically be highest in the periods just before and just after a medical visit (MacLaughlin et al., 2005). Therefore, if patients require relatively infrequent medical visits (e.g., those taking oral hormonal breast cancer therapy), the likelihood for nonadherence to medication may be increased. For these particular patients, ensuring consistent follow-up and enhancing communication between the nurse and patient at each visit are even more important.

Having an ongoing relationship with a particular nurse or other healthcare provider may significantly improve adherence to therapy, particularly for patients who lack support at home. Enhancing the quality of communication could improve patients’ ability to adhere (Blasdel & Bubalo, 2006); it has been suggested that patient and family education may be the most critical factor for successful treatment (Moore, S., 2007). At each visit, patients could receive reinforcement of the clinical benefits of adherence to their prescribed treatment and be reminded of the clinical reasons for taking their oral medication as directed.

In addition, following up with the patient or caregiver afterwards (e.g., a quick phone call) might intercept long-term adherence issues before they arise. Patients who feel that they have a quality relationship with their healthcare providers and place trust in their advice are more likely to adhere to their recommendations (Chia et al., 2006; Kennedy et al., 2008).

Better Management to Minimize Treatment-Related Side Effects

Nurses can play a significant role in managing adverse events by talking to patients about potential side effects and notifying their physicians when necessary. In addition, educating patients at the beginning of their treatment about early recognition of side effects and the importance of reporting their symptoms (Moore, 2005) may leave patients feeling less anxious and more prepared. Nurses can also reinforce their understanding that dose reductions and delays in therapy are expected (Moore, 2005). Additional support, such as having patients encourage family members to be part of the treatment process and giving patients regularly scheduled reminders for their appointments, may improve adherence.

Alternative Medication Regimens

Objectively measuring, monitoring, and improving medication adherence is difficult because of individual patient behavior (Simenson, 2006). Reasons for nonadherence are multifactorial, and any single intervention is unlikely to have a major effect (Heidenreich, 2004). In addition, little evidence supports that medication adherence can be consistently improved with the resources available in the clinical setting (Haynes, Ackloo, Sahota, McDonald, & Yao, 2008). Adherence to oral breast cancer therapy may pose a challenge to some patients. Partridge, Wang, Winer, and Avorn (2003) found that 77% of patients were adherent during their first year of tamoxifen therapy, but only 50% of patients remained adherent at the fourth year of follow-up (Partridge et al., 2003).

Patients who have difficulty maintaining adherence may require more intensive strategies, such as IV infusion or intra-muscular (IM) injection. IV therapy takes place in a doctor’s office; therefore, adherence is ensured if the patient keeps the scheduled appointment and the correct or optimal dose is given. Of the patients who preferred IM injection as their method of administration of endocrine treatment in a breast cancer study, 43% stated that this method ensured they received their treatment (Fallowfield et al., 2006). If an oral and an IV breast cancer treatment are equivalent (e.g., oral capetibidine and IV 5-fluorouracil) and the patient does not adhere to oral therapy for any of the reasons discussed, the IV treatment may be more suitable. IV therapies also may be preferred because of financial reasons, as many patients cannot afford oral medications. Other patients, such as the homeless, may lack resources for safe procurement and storage of oral medications and come to clinics to receive IV or IM treatment. Many new combination regimens under investigation include oral and IV therapies; therefore, patients still need to come into the healthcare setting. This provides an opportunity to check on adherence.

Conclusion

Adherence is a significant issue for oral therapy for breast cancer. However, many of the published adherence rates are based on studies assessing adherence to tamoxifen regimens. Healthcare providers and researchers should err on the side of caution when applying the conclusions from these studies to adherence with oral chemotherapy in general because these types of therapy are given in very different ways, with chemotherapies typically

Figure 2. Patient Information to Promote Adherence


- What condition the medicine was prescribed to treat
- What the medicine is, why it is needed, and how it works in the body
- Why the medicine was selected
- The dosage schedule and related instructions about how to take the medicine (before eating, with food, etc.)
- Whether the medicine will work safely with other medicines being taken (both prescription and nonprescription medicines)
- What to do if doses are missed or delayed
- The common adverse effects that may occur and what to do about them
being given over shorter regimens than the endocrine therapies. As more data with newer oral therapies become available, a fuller understanding of adherence to oral chemotherapy regimens may emerge.

Nonetheless, this is a critical issue as suboptimal adherence to medication regimens impacts clinical benefit and can result in treatment resistance and disease progression. Oral cancer therapies will be effective only if patient adherence is successful. Additional research into improving adherence is necessary for optimal use of oral therapies because a limited amount of reports have been published on methods to improve adherence among patients who have breast cancer. Nurses, in collaboration with other healthcare professionals, play an important role in monitoring adherence. Identifying potential barriers and implementing intervention strategies would help to enhance adherence and, therefore, improve clinical outcomes. If barriers to adherence with oral therapies persist, adherence and the optimal dose of medication can be consistently ensured with IV therapy if that alternative is available.

The author takes full responsibility for the content of the article. The author is a member of the speakers bureau for Roche Laboratories. The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the author, planners, independent peer reviewers, or editorial staff.

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