

Adherence to Oral Endocrine Therapy for Breast Cancer: A Nursing Perspective

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Many factors contribute to the success or failure of adjuvant therapy, but perhaps one of the most critical is treatment adherence. Patients do not adhere to prescribed therapy for a variety of reasons, and each one should be uncovered and addressed or managed accordingly to maintain therapeutic levels and give patients the best chance for positive outcomes. Nurses are well positioned to play a central role in promoting adherence by ensuring that patients understand the need for treatment and by identifying any underlying causes of nonadherence to therapy. When the issues are identified and addressed effectively, patients' chances for successful clinical outcomes are greatly improved. This article summarizes the issues surrounding adherence, paying specific attention to adjuvant endocrine therapy for breast cancer, and outlines strategies to reduce nonadherence that nurses can incorporate into clinical practice.

Adherence is one of the most important factors contributing to the success or failure of therapeutic interventions in chronic diseases. Generally defined, *adherence* reflects the extent to which patients follow a medical action plan to achieve a desired therapeutic goal, whether to get regular exercise, lose weight, stop smoking, or take oral medications (Haynes, McDonald, & Garg, 2002; Hill, 2005). By current estimates, 30%–60% of patients show some degree of nonadherence to prescribed oral medication, even to the point of failing to fill their prescriptions (as many as 50% of all prescriptions may go unfilled) (Barber, 2002; Cramer, 2002; Haynes et al., 2002). Other terms, including *primary nonadherence* (failing to begin a prescribed therapy), *dose omission* versus *incorrect timing of doses*, and *intentional nonadherence* versus *unintentional nonadherence*, sometimes are used to describe more specific aspects of nonadherence.

Adherence can be a major determinant of the therapeutic efficacy of a medication regimen. A treatment regimen with significant side effects may diminish a patient's quality of life (QOL) and consequently undermine adherence, whereas a regimen that relieves disease symptoms is expected to improve QOL and promote adherence (Dunbar-Jacob et al., 2000). In chronic conditions such as hypertension, diabetes, and hyperlipidemia, when the treatment goal is control rather than cure, adherence is especially problematic. In contrast, adherence to medication is higher among patients with acute diseases than among those with chronic diseases, as the sense of urgency tends to evaporate with long or indefinite treatment durations. Clearly, patients with any chronic or long-term condition can become discouraged or apathetic when facing long or indefinite treatment durations,

At a Glance

- ◆ Adherence to oral endocrine therapy in the treatment of breast cancer has been largely overlooked; nurses can have positive effects on patient outcomes when they recognize and manage nonadherence issues.
- ◆ In addition to their clinical expertise, nurses are adept at procuring essential feedback from patients, thereby giving the medical team further insight regarding the likelihood of adherence to a prescribed regimen.
- ◆ Continuity of health care and consistency of dialogue between patients and caregivers are important for improving adherence; the key is finding a way to reach all patients, especially in underserved populations, for regular communication and follow-up.

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particularly when the benefits of treatments are intangible and therefore unaccompanied by positive reinforcement from an improved sense of well-being.

Cancer is not a chronic disease in the technical sense of the word, but some malignancies have become long-term conditions that benefit from prolonged treatment, particularly with the advent of targeted oral therapies that confer fewer cytotoxic systemic side effects. Adjuvant endocrine therapy of breast cancer is a case in point. In that setting, women are expected to take an oral agent on a daily basis for at least five years. Because breast cancer can be life threatening in the short term, healthcare providers had assumed that all women would be highly motivated to adhere to treatment regimens that would significantly lower their risk for disease recurrence (Waterhouse, Calzone, Mele, & Brenner, 1993). However, many women consider themselves “cured” after initial surgery, chemotherapy, and/or radiotherapy. Such women may fail to recognize the benefits of adjuvant endocrine therapy and take a more relaxed view of the long-term endocrine therapy that follows (Davidson, Vogel, & Wickerham, 2006).

Benefits of Oral Endocrine Therapy

The importance of adjuvant endocrine therapy in improving outcomes of women with hormone receptor-positive breast cancer is clear. Consider the findings of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), which reviewed data on adjuvant tamoxifen therapy in approximately 30,000 patients with breast cancer with estrogen receptor-positive disease or unknown estrogen receptor status.

- Adjuvant tamoxifen therapy for five years significantly reduced the 10-year cumulative disease recurrence rate as compared with no adjuvant endocrine therapy in node-negative (from 36% to 21%, $p < 0.00001$) and node-positive (from 56% to 40%, $p < 0.00001$) patients (EBCTCG, 1998).
- More importantly, adjuvant tamoxifen therapy for five years significantly reduced the 10-year mortality rate (death from any cause) in node-negative (from 27% to 21%, $p < 0.00001$) and node-positive (from 50% to 39%, $p < 0.00001$) patients (EBCTCG, 1998).

The clinical benefit of adjuvant endocrine therapy has been reinforced by recent studies with aromatase inhibitors. The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial showed that adjuvant treatment with anastrozole for five years further extends disease-free survival of postmenopausal women with hormone receptor-positive early breast cancer (Howell et al., 2005). The MA.17 trial of letrozole showed that extending adjuvant therapy beyond five years of tamoxifen by using the aromatase inhibitor letrozole increased disease-free survival and, among patients with node-positive disease, increased overall survival as well (Goss et al., 2005). Additionally, the Intergroup Exemestane Study (IES) showed that switching to exemestane after two to three years of tamoxifen treatment significantly improved disease-free survival compared with five years of tamoxifen (Coombs et al., 2004). Therefore, postmenopausal patients diagnosed with hormone receptor-positive early breast cancer should expect to remain on some form of endocrine therapy for a minimum of five years to maximize their chances to remain free of cancer.

Adherence to Endocrine Therapy in Clinical Trials

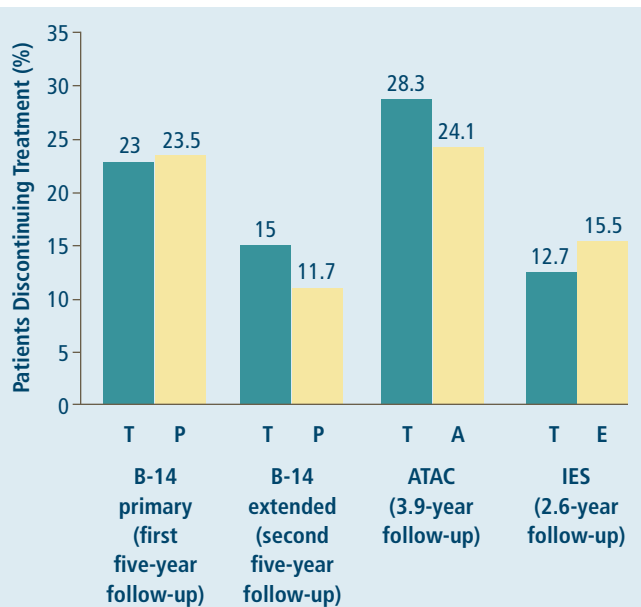
Clinical trials provide an ideal setting for promoting adherence to treatment. Patients are monitored closely at regularly scheduled visits, often receiving encouragement and reminders from medical staff to adhere to study protocols and to take study medications. Moreover, patients enrolled in clinical trials may be more motivated to adhere to treatment than the general patient population in clinical practice settings. Nevertheless, nonadherence rates in major clinical trials are significant, typically resulting from adverse events, withdrawn consent, protocol violations, side effects, or lack of efficacy.

Data from clinical trials in other chronic diseases reflect typical patient habits regarding adherence. The Long-Term Intervention With Pravastatin in Ischaemic Disease (LIPID) study evaluated statin therapy on mortality risk in patients with coronary heart disease (LIPID Study Group, 1998). By the end of the six-year study, 19% of patients originally assigned to pravastatin and 24% of those assigned to placebo had permanently stopped taking their study drugs. The United Kingdom Prospective Diabetes Study (UKPDS) evaluated the impact of blood glucose control on the risk of diabetes-related complications in patients with newly diagnosed type 2 diabetes (UKPDS Group, 1995). By year 3, 10% of patients initially assigned to receive oral sulfonylureas and 11% of those assigned to metformin were no longer taking their treatment medications. Thus, adherence may be problematic even in major clinical trials.

Nonadherence rates of 12% or higher have been observed in clinical trials of adjuvant endocrine therapy (see Figure 1). Overall, a recent review of the literature showed that about 25% of all patients in clinical trials of adjuvant hormonal therapy (tamoxifen and aromatase inhibitors) prematurely discontinued treatment (Chlebowski & Geller, 2007). Early discontinuation rates were even higher in prevention trials with tamoxifen (20%–46%).

More specifically, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 evaluated adjuvant tamoxifen therapy in node-negative, estrogen receptor-positive breast cancer. Two percent of patients failed to even start their study therapy (Fisher et al., 1996). In addition, 23% of patients assigned to tamoxifen and 23.5% assigned to placebo discontinued study treatment during the first five years of scheduled therapy. Many simply chose to discontinue treatment (10.2% and 13.0%, respectively), whereas others discontinued treatment because of adverse events or medical reasons (11.2% and 8.2%, respectively). In the five-year extension of the NSABP B-14 adjuvant trial, which included patients who were free of disease after the primary trial, 15% of tamoxifen-treated and 11.7% of placebo-treated patients discontinued therapy during the second five-year period, mainly because of withdrawal from the study (Fisher et al., 1996).

Similar nonadherence rates were reported in recent trials of aromatase inhibitors. In ATAC, 24.1% of patients assigned to anastrozole and 28.3% assigned to tamoxifen discontinued therapy within 3.9 years (Baum et al., 2003). By the 5.7-year follow-up, adverse events had led to discontinuation of 11.1% and 14.3% of patients in the anastrozole and tamoxifen groups,



Note. Shown are the percentages of patients who discontinued study treatment and the corresponding follow-up for each study.

A—anastrozole; ATAC—Arimidex, Tamoxifen, Alone or in Combination trial; E—exemestane; IES—Intergroup Exemestane Study; P—placebo; T—tamoxifen

Figure 1. Rates of Nonadherence to Adjuvant Endocrine Therapy in Major Clinical Trials

Note. Based on information from Baum et al., 2003; Coombes et al., 2004; Fisher et al., 1996.

respectively (Howell et al., 2005). Similarly, in IES, 15.5% of patients allocated to exemestane and 12.7% on tamoxifen had stopped therapy by 2.6 years, with 5.8% and 5.1% citing adverse side effects, respectively (Coombes et al., 2004).

Taken together, the studies show that many women stop taking adjuvant endocrine therapy mostly because of adverse events but also other reasons, captured in clinical trials as “withdrawal of consent.” Notably, the figures do not include the frequency of missed doses or medication holidays, which represent another form of nonadherence.

Breast cancer prevention trials, which study the ability of endocrine therapy to prevent or delay breast cancer in healthy but high-risk women, also show significant levels of nonadherence. In the Royal Marsden Hospital trial, 39.8% of women assigned to tamoxifen and 30.5% assigned to placebo stopped treatment prematurely (Powles et al., 1998). Adverse events were responsible for discontinuation in most cases (25.6% and 14.1%, respectively), but “nontoxic” reasons also were cited frequently (14.2% and 16.4%, respectively). Similarly, in the NSABP-P1 prevention trial, 23.7% of women allocated to tamoxifen and 19.7% on placebo stopped treatment prematurely (Fisher et al., 1998). Overall, 7.2% of study participants withdrew their consent and stopped treatment. Thus, the risk for occurrence or recurrence of breast cancer in high-risk patients may not be a sufficiently strong motivator in all women to ensure adherence to endocrine therapy.

Adherence to Endocrine Therapy in Clinical Practice

Adherence can be estimated in clinical practice by a variety of methods, including self-report questionnaires, telephone interviews, prescription refill data, manual counting of unused medication, and electronic pill dispensers. Many such methods have been used to estimate adherence to tamoxifen in clinical practice (Demissie, Silliman, & Lash, 2001; Fink, Gurwitz, Rakowski, Guadagnoli, & Silliman, 2004; Grunfeld, Hunter, Sikka, & Mittal, 2005; Lash, Fox, Westrup, Fink, & Silliman, 2006; Martin, Barghout, & Hutchins, 2006; Murthy, Bharia, & Sarin, 2002; Owusu et al., 2006; Partridge, Wang, Winer, & Avorn, 2003; Partridge, LaFountain, Taylor, & Asnis-Alibozek, 2006; Waterhouse et al., 1993; Yen et al., 2004) (see Table 1). Self-report questionnaires, often considered the least reliable of the measurement methods, identify 12%–24% of patients as missing one or more tamoxifen doses per week (Grunfeld et al.; Murthy et al.). Telephone interviews conducted at varying times following primary surgery have shown that 15%–17% of patients discontinued tamoxifen after two to three years of therapy, whereas 31% failed to complete their prescribed course of adjuvant therapy at five years (Demissie et al.; Fink et al.; Lash et al.).

Reviews of medical and pharmacy records found that 21% of women with ductal carcinoma in situ stopped tamoxifen by year 3, and 50% of those with early breast cancer stopped treatment by year 5 (Owusu et al., 2006; Yen et al., 2004). In a retrospective analysis of a large prescription-refill insurance database, 23% of women were nonadherent during their first year of adjuvant tamoxifen therapy (they had prescription refills covering fewer than 80% of eligible days) (Partridge et al., 2003). Similarly, in an analysis of another database that linked medical, prescription, and enrollment health information, 10% of a cohort of nearly 13,700 women starting adjuvant therapy with tamoxifen had a gap in treatment of more than 60 days (Martin et al., 2006). Recent data also suggest similar results in patients who received the aromatase inhibitor anastrozole (Partridge et al., 2006). The study from a single, large health plan of longitudinal claims of 1,498 women with early breast cancer showed that one in five may have been suboptimally adherent to adjuvant anastrozole during the first year of treatment.

Self-reports of adherence typically are higher than those found by pill counts or electronic means. In a study of 26 women receiving tamoxifen therapy, Waterhouse et al. (1993) compared patient self-reports with pill counts and a Medication Event Monitoring System (MEMS) (Apex Corp.), which records each opening (date, time, and duration) of a medication bottle. The patients were not informed beforehand that adherence would be monitored. Patients were defined as nonadherent if they took fewer than 80% of the prescribed doses of tamoxifen. The self-report questionnaire identified about 2% of nonadherent patients, whereas pill counting found a nonadherence rate of 17%. Taking into account dose omissions and dosing-interval errors, MEMS found that 75% of the cohort was less than 80% adherent to the tamoxifen regimen. The data illustrate that patients tend to over-report their adherence to adjuvant endocrine therapy and that the method used to measure adherence is extremely important.

Table 1. Adherence to Hormonal Therapy for Breast Cancer in Clinical Practice

THERAPY AND SAMPLE SIZE	METHOD OF ADHERENCE MEASUREMENT	MEASUREMENT DURATION	RESULTS
TAMOXIFEN			
53	Self-report questionnaire	6 months	24% missed ≥ 1 dose per week (Murthy et al., 2002).
110	Self-report questionnaire	1 week	12% missed ≥ 1 dose in previous week (Grunfeld et al., 2005).
189	Telephone interviews at 5, 21, and 33 months after primary surgery	About 3 years	15% discontinued (Demissie et al., 2001).
516	Telephone interviews at 3, 6, 15, and 27 months after primary surgery	2 years 5 years	17% discontinued by two years (Fink et al., 2004). 31% failed to complete prescribed five years (Lash et al., 2006).
94	Chart review	3 years	21% discontinued (Yen et al., 2004).
1,080	Medical and pharmacy records	5 years	50% discontinued by five years (Owusu et al., 2006).
2,378	Prescription-refill insurance database	1 year	23% had $< 80\%$ of eligible days covered by prescription refills (Partridge et al., 2003).
16,900	Commercial research databases	12 months	10% were not persistent (had gap of > 60 days in prescription refills) (Martin et al., 2006).
24	Self-report (SR) versus pill count (PC) versus Medication Event Monitoring System (MEMS)	3 months (mean)	$< 80\%$ were adherent by criteria of dose omission and dosing-interval errors (Waterhouse et al., 1993). SR: About 2% PC: 17% MEMS: 75% (21% by criterion of dose omission alone)
ANASTROZOLE			
1,498	Prescription-refill insurance database	3 years	85% with early breast cancer were still filling prescriptions by 12 months. 19% had less than 80% of days covered. Mean number of days covered decreased over time: year 1 (86%), year 2 (82%), year 3 (79%) (Partridge et al., 2006)

Predictors of Nonadherence

Investigators have tried to identify predictors of nonadherence to develop interventions to improve adherence. In doing so, they have found that age, gender, race, education level, socioeconomic status, disease state, and disease severity do not correlate predictably with adherence (Stephenson, Rowe, Haynes, Macharia, & Leon, 1993). Moreover, physicians are not able to reliably predict which patients will adhere to a prescribed regimen (Gilbert, Evans, Haynes, & Tugwell, 1980).

Figure 2 lists the signs and predictors of poor adherence, categorized according to whether patients, healthcare professionals, or the healthcare system play a primary role. Past adherence also is considered to be a key determinant of future adherence (De Geest, von Renteln-Kruse, Steeman, Degraeve, & Abraham, 1998). By recognizing which factors may predict nonadherence, nurses may be able to identify patients who are most likely to be nonadherent to adjuvant endocrine therapy, which would allow them to provide individualized support to help ensure successful treatment.

Patients' beliefs about their prescribed medications are powerful predictors of adherence to drug regimens (Brown et al., 2005). In the Health Belief Model, patient perceptions

of susceptibility, severity, benefits, barriers, and self-efficacy combine with cues to action to determine adherence behavior. In a study of 110 tamoxifen-treated patients with early breast cancer, nonadherent patients were more likely to believe nothing could be gained from taking tamoxifen (Grunfeld et al., 2005). Many patients get much of their information about treatment from nonmedical sources, such as the lay press or friends and family members, which may contribute to wariness regarding prescribed medications. Other predictors of nonadherence include Bandura's concept of self-efficacy, which denotes confidence in one's ability to perform a certain task in variable circumstances (De Geest et al., 1998; Lev, 1997). Conscientiousness and estimated IQ also have been shown to correlate with adherence (Stilley, Sereika, Muldoon, Ryan, & Dunbar-Jacob, 2004). In one study of patients with early breast cancer, simply forgetting to take medication accounted for 18% of poor adherence to tamoxifen regimens (Grunfeld et al.).

Psychological problems, particularly depression and anxiety, and lack of social support also seem to contribute to nonadherence (De Geest et al., 1998; Stilley et al., 2004). In a study of patients with early breast cancer, the prevalence of depression and/or anxiety in the first year after diagnosis was

48%, decreasing to 15% by the fifth year (Burgess et al., 2005) (see Figure 3). However, medication nonadherence tends to increase over time, suggesting that depression and anxiety may have a reverse correlation to adherence in the first years of adjuvant endocrine therapy (Partridge et al., 2003). As time goes by and depression and/or anxiety are relieved, patients seem to be less likely to comply with therapy.

Finally, complex dosing regimens and inadequate follow-up can contribute to nonadherence (De Geest et al., 1998). Patients are more likely to be nonadherent when they are prescribed medications that must be taken three or more times each day.

How Healthcare Professionals Can Help: Keep It Simple and Communicate

Poor patient-provider communication can lead to misunderstandings about why and how to take medications. If a patient does not understand why a certain medication is necessary, his or her confidence in the treatment plan may be undermined. For participants in the International Breast Cancer Intervention Study-I prevention trial, their inherited risk of breast cancer was surprisingly unrelated to tamoxifen adherence, suggesting that medication-taking behavior may be guided more by subjectively perceived risk than by actual risk (Maurice, Howell, Evans, O'Neil, & Scobie, 2006). Physicians and nurses have an opportunity to educate their patients about the differences between perceived and actual risk, thus stressing the importance of following their regimens through to conclusion.

Interestingly, patient dissatisfaction with the treating physician has been correlated with primary medication nonadherence. In a large sample of telephone survey respondents who had received prescriptions during the previous year, physician dissatisfaction was reported as a major reason for nonadherence (Wroth & Pathman, 2006). The role of the oncology nurse is paramount in augmenting patient-provider interaction, whether via office visits or by follow-up telephone calls. For example, a nurse can solicit questions that a patient was too intimidated to ask without encouragement. In addition, information that seems obvious to physicians and nurses is not always evident to patients; consequently, simple advice provided by a nurse can go a long way toward improving adherence.

Rising medication costs and busy schedules are two additional deterrents to adherence (Bond & Hussar, 1991; De Geest et al., 1998). Discussing potential solutions to those problems can contribute to improved adherence. For example, automatic mail-order prescription refills eliminate the inconvenience of ordering and retrieving medications from local retail pharmacies and usually are more cost effective. Discount drug programs are available to many older and low-income patients, which can remove a key barrier to adherence in those subgroups. In addition, pharmaceutical companies often have drug programs for patients in need.

The following strategies may help to improve patient adherence.

Patient

Chronic disease (long treatment duration)
Missed medical appointments
Unfilled prescriptions
Lack of expected therapeutic response
History of poor adherence (e.g., to mammography screening)
Lack of belief in treatment
Lack of support from family and friends
Psychological problems, particularly depression

Healthcare Professional

Complex dosing regimen
Inadequate follow-up
Poor patient-provider communication

Healthcare System

Adverse effects from medication
High cost of medication
Prescriptions filled at retail pharmacies instead of by mail order

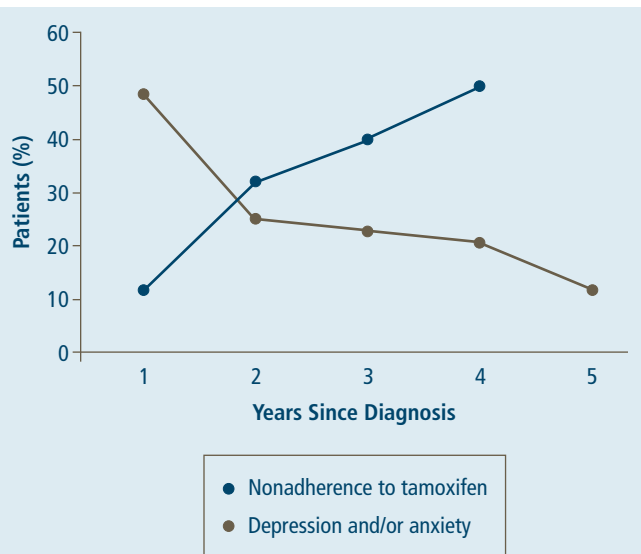
Figure 2. Signs and Predictors of Poor Adherence

Note. From "Adherence to Medication," by L. Osterberg and T. Blaschke, 2005, *New England Journal of Medicine*, 353(5), p. 487. Copyright 2005 by the Massachusetts Medical Society. Adapted with permission.

- Assess the patient's understanding of the need for the prescribed treatment and its goals.
- Provide written information about the treatment.
- Review potential side effects of the treatment and develop management strategies, as needed.
- Explore the patient's psychosocial dynamics, including prescription coverage, access to filling prescriptions, and support systems.
- Provide the patient with professional contact information, especially a phone number, in the event of questions, side effects, or concerns.
- Schedule follow-up contacts on a regular basis to reassess and reiterate the treatment plan.
- Provide a list of organizations and support groups that the patient can consult for more information and advice.

Improving Communication Specific to Endocrine Therapy

Physicians may underestimate and therefore fail to communicate to patients the burden of side effects that accompany endocrine therapy (Fallowfield, 2005). In a cohort of 110 tamoxifen-treated patients with early breast cancer, 46% of nonadherent subjects attributed their lapses in compliance to an increase in side effects, specifically hot flashes, night sweats, concentration or memory difficulties, sleep problems, emotional problems (e.g., anxiety, panic, depression), weight gain, and loss of libido (Grunfeld et al., 2005). In an Internet survey posted by the Y-ME National Breast Cancer Organization, only 57.4% of survey respondents rated their ability to adhere to endocrine therapy as excellent (not missing a single dose), whereas 24.1% believed their adherence would improve if treatment-related



Note. Nonadherence rates were estimated based on prescription refills for a cohort of 492 patients who filled a first prescription for tamoxifen in 1991. Nonadherence was defined as having < 80% of eligible days during a year covered by a filled tamoxifen prescription. The annual incidence of depression and/or anxiety was estimated in a cohort of 202 women and was defined by the percentage with at least one episode of depression, anxiety, or both during each one-year period.

Figure 3. Nonadherence Rates for Adjuvant Tamoxifen Therapy in Clinical Practice and Incidence of Depression and/or Anxiety

Note. Based on information from Burgess et al., 2005; Partridge et al., 2003.

side effects were managed better (Kirk & Hudis, 2006). The tendency of physicians to ignore or trivialize side effects that are not life threatening but do impact QOL will almost certainly discourage patients from volunteering tolerance problems, thus increasing the likelihood of nonadherence (Fallowfield). If side effects are the main reason for nonadherence to adjuvant endocrine therapy, then their prevention or management should be top priority.

Nursing Interventions for Improving Adherence

As previously stated, adherence to long-term treatment is improved by more convenient care, information, reminders, self-monitoring, reinforcement, counseling, family therapy, psychological therapy, crisis intervention, manual telephone calls, and supportive care (Haynes et al., 2005). Patients generally feel more relaxed and comfortable communicating with nurses than with physicians. In addition to their clinical expertise, nurses are adept at building trust and procuring essential feedback from patients and from support partners, thus giving the medical team further insight as to the likelihood of adherence to prescribed regimens.

Physicians should strive to cultivate an approach to patients that is open and empathetic rather than dominant or judgmental (De Geest et al., 1998). Involving nurses in such an integral role helps to foster more open relationships. This may be particularly important when discussing prescribed medications, because patients typically forget about half of what physicians tell them (Turner & Williams, 2002) and may not fully understand why medications are prescribed or how and when they should be taken. Giving patients simple written instructions would go a long way in overcoming the communication gap (Smith, 1989). A nurse educator should intercede after each patient-physician visit to review the prescribed regimen. At that critical juncture, nurses can stress the importance of adherence in light of the physician's risk assessment.

At follow-up visits, nurses can reinforce the patient education that was given at the start of adjuvant endocrine therapy. They can address patient adherence by asking questions or administering an in-office questionnaire, suggesting interventions if necessary. The Modified Morisky Scale may be particularly useful in such a setting (Morisky, Green, & Levine, 1986). It consists of the following questions.

- Do you ever forget to take your medication?
- Are you careless at times about taking your medication?
- When you feel better, do you sometimes stop taking your medication?
- Sometimes if you feel worse when you take your medication, do you choose to stop taking it?

One point is assigned for each affirmative answer. Patients with scores of 0 or 1 typically show high levels of adherence, whereas those with higher scores are more likely to require interventions to improve adherence. Additional questions that can be used to assess adherence include: Do you know the long-term benefit of taking your medication? Do you sometimes forget to refill your prescription on time?

At follow-up visits, nurses also may solicit any remaining questions about therapy, including those that patients might hesitate to bring up, such as sexual problems (Jenkins, Fallowfield, & Poole, 2001) and financial worries. Patients who are involved in decision making and who are offered management strategies for side effects will be more likely to follow their therapy routines reliably, especially when they believe their concerns are validated.

Patients may be inclined to stop treatment because of adverse events; nurses can play an important role in managing adverse events by talking with patients and notifying a doctor of potential issues. In addition, patients should be unambiguously instructed to contact the nursing staff and clinicians at the first sign of an adverse event. Dose modification, when possible, can prevent many patients from discontinuing medications.

Nurses also play a critical role in triaging phone calls. When patients call regarding adverse events, nurses often can provide suggestions to help resolve simple issues or take detailed information for more pressing problems. A patient's medication list must be recorded accurately, as it is instrumental in allowing the treating physician to assess potential drug interactions with a newly prescribed endocrine agent.

In addition to talking to patients during clinical visits, nurses can suggest groups and organizations to which patients can turn for support and information between office visits.

The Extended Role of Nurses in Promoting Adherence

Oncology nurses who administer IV chemotherapy in a clinic's infusion area might use the opportunity to establish rapport with patients with breast cancer and teach them about endocrine therapy when patients are to be offered endocrine therapy as part of their treatment regimens (Hartigan, 2003). Thus, when chemotherapy is completed, patients will better recognize the need for adjuvant endocrine therapy as the next step in their overall treatment plans. Verbal discussions about endocrine therapy could be supplemented with written materials and links to Web sites of the many breast cancer organizations. Importantly, nurses need to be adaptable in their approach, given the varying socioeconomic and educational levels of patients.

For example, carefully explaining the difference between the widely reported side effects of hormone-replacement therapy in menopausal women and those associated with endocrine therapy for breast cancer may be helpful. Confusion or misinformation about hormonal therapies may preclude some patients from starting therapy.

Another misconception that must be addressed is improper use of an agent (e.g., taking several pills at once to make up for missed days, taking every other pill to save money). Healthcare providers also must consider that patients may not want to admit that they are not taking their medications as prescribed or that they have missed doses. Therefore, ask probing questions regarding medication-taking habits.

Economic concerns may be particularly prevalent in patients on Medicare. Although Medicare pays for 75% of initial drug costs, up to \$2,250, a complete lack of coverage exists between \$2,251 and \$3,600, after which 95% of drug costs are paid. Because more than a quarter of patients on Medicare are projected to fall within the nonreimbursed range, nurses may encounter patient bias toward saving money through inappropriate means (DeNatale, 2007). As more targeted therapies emerge, cost will become an even greater cause for concern.

Continuity and consistency of health care are important for improving adherence, especially with chronic conditions (De Geest et al., 1998). An ongoing relationship with a particular nurse may significantly bolster adherence to therapy, especially for patients lacking support from home. The key is finding a way to reach all patients, especially the underserved, for consistent follow-up. Individualized communication plans and learning strategies can be devised by nurse-patient brainstorming. Depending on a practice's capabilities and patient base, communication strategies may consist of phone calls, e-mail, contact with a family member or neighbor, or other ways in which patient and nurse can keep in touch with each other. To help educate patients, nurses should identify each patient's preferred learning style; for instance, does the patient prefer reading material? One-on-one discussions? Talking with other patients? To illustrate, a study of raloxifene treatment for osteoporosis showed that MEMS-evaluated adherence increased by 57% with patient monitoring at quarterly visits by nurses who assessed adherence and QOL (Clowes, Peel, & Eastell, 2004).

Cognitive impairment is a risk factor for misunderstanding directions regarding medication regimens (Bergman-Evans, 2006). Chemotherapy has been linked to cognitive impairment,

at least in the short term, whereas cognitive deficits resulting from endocrine therapy are more conjectural (Jenkins, Shilling, Fallowfield, Howell, & Hutton, 2004; Jenkins et al., 2006). By having a more convivial relationship with patients, nurses can be sensitive to signs of cognitive impairment in patients with breast cancer receiving adjuvant therapy and can use tools such as the Mini-Mental State Exam to detect it (Bergman-Evans). Patients identified as having verbal deficits might be better served by nonverbal adherence interventions, such as pill boxes and medication calendars.

An estimated 22%-50% of patients with breast cancer meet criteria for clinical depression, and 3%-19% have symptoms of post-traumatic stress disorder (PTSD) (Classen et al., 2001). Focusing on the "avoidance" dimension of PTSD, research has suggested that not taking prescribed medication may allow patients who are traumatized by illness to avoid being reminded of it. However, some investigators have reported that only a small proportion (3%-4%) of patients with breast cancer meet stringent criteria for PTSD, in which case psychological distress rather than trauma may provide a better framework for understanding their adherence behaviors (Green et al., 1998; Palmer, Kagee, Coyne, & DeMichele, 2004).

Conclusions

The reasons for nonadherence vary, ranging from treatment-related side effects to lack of confidence in prescribed medications. As a first step, nurses must inform patients about the proven benefits of adjuvant endocrine therapy in early breast cancer (lower disease recurrence and lower mortality) and then correlate the better clinical outcomes with higher levels of adherence. Communicating the correlation is a motivating factor for patients to adhere to prescribed regimens. Although patients ultimately decide whether to follow prescribed regimens, nurses and other healthcare providers can have a significant influence on their final decisions. Endocrine therapies are associated with a long and extensive body of evidence regarding adherence compared to other anticancer therapies. Nurses can benefit from the information in terms of what to look for when monitoring and reinforcing adherence to treatment. Nurses have the potential to play an important role in identifying non-adherent patients, tailoring interventions to individuals, and motivating patients to strive for successful outcomes of their endocrine therapy. The caring behavior of nurses as perceived by patients with cancer involves emotional, informational, and practical support that is based on patient needs (Boman, Andersson, & Bjorvell, 1997). Nurses must continue to provide and improve upon those qualities as well as their professional oncology knowledge, attitudes, and skills for the sake of their patients (Liu, Mok, & Wong, 2006).

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References

- Barber, N. (2002). Should we consider non-compliance a medical error? *Quality and Safety in Health Care, 11*(1), 81-84.
- Baum, M., Buzdar, A., Cuzick, J., Forbes, J., Houghton, J., Howell, A., et al. (2003). Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial efficacy and safety update analyses. *Cancer, 98*(9), 1802-1810.
- Bergman-Evans, B. (2006). AIDES to improving medication adherence in older adults. *Geriatric Nursing, 27*(3), 174-182.
- Boman, L., Andersson, J.U., & Bjorvell, H. (1997). Needs as expressed by women after breast cancer surgery in the setting of a short hospital stay. *Scandinavian Journal of Caring Sciences, 11*(1), 25-32.
- Bond, W.S., & Hussar, D.A. (1991). Detection methods and strategies for improving medication compliance. *American Journal of Hospital Pharmacy, 48*(9), 1978-1988.
- Brown, C., Battista, D.R., Bruehlman, R., Sereika, S.S., Thase, M.E., & Dunbar-Jacob, J. (2005). Beliefs about antidepressant medications in primary care patients: Relationship to self-reported adherence. *Medical Care, 43*(12), 1203-1207.
- Burgess, C., Cornelius, V., Love, S., Graham, J., Richards, M., & Ramirez, A. (2005). Depression and anxiety in women with early breast cancer: Five year observational cohort study. *BMJ, 330*(7493), 702-705.
- Chlebowski, R.T., & Geller, M.L. (2007). Adherence to endocrine therapy for breast cancer. *Oncology, 71*(1-2), 1-9.
- Classen, C., Butler, L.D., Koopman, C., Miller, E., DiMiceli, S., Giese-Davis, J., et al. (2001). Supportive-expressive group therapy and distress in patients with metastatic breast cancer: A randomized clinical intervention trial. *Archives in General Psychiatry, 58*(5), 494-501.
- Clowes, J.A., Peel, N.F.A., & Eastell, R. (2004). The impact of monitoring on adherence and persistence with antiresorptive treatment for postmenopausal osteoporosis: A randomized controlled trial. *Journal of Clinical Endocrinology and Metabolism, 89*(3), 1117-1123.
- Coombes, R.C., Hall, E., Gibson, L.J., Paridaens, R., Jassem, J., De-lozier, T., et al. (2004). A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *New England Journal of Medicine, 350*(11), 1081-1092.
- Cramer, J.A. (2002). Effect of partial compliance on cardiovascular medication effectiveness. *Heart, 88*(2), 203-206.
- Davidson, B., Vogel, V., & Wickerham, L. (2006). How conversations about adjuvant hormonal therapy differ from 'typical' oncology discussions: Results of an observational linguistic study [Abstract]. Proceedings of the 2006 American Society of Clinical Oncology annual meeting. *Journal of Clinical Oncology, 24*(18, Suppl.), 6141.
- De Geest, S., von Renteln-Kruse, W., Steeman, E., Degraeve, S., & Abraham, I.L. (1998). Compliance issues with the geriatric population: Complexity with aging. *Nursing Clinics of North America, 33*(3), 467-480.
- Demissie, S., Silliman, R.A., & Lash, T.L. (2001). Adjuvant tamoxifen: Predictors of use, side effects, and discontinuation in older women. *Journal of Clinical Oncology, 19*(2), 322-328.
- DeNatale, M.L. (2007). Understanding the Medicare Part D prescription program: Partnerships for beneficiaries and health care professionals. *Policy, Politics, and Nursing Practice, 8*(3), 170-181.
- Dunbar-Jacob, J., Erlen, J.A., Schlenk, E.A., Ryan, C.M., Sereika, S.M., & Doswell, W.M. (2000). Adherence in chronic disease. *Annual Review of Nursing Research, 18*, 48-90.
- Early Breast Cancer Trialists' Collaborative Group. (1998). Tamoxifen for early breast cancer: An overview of the randomised trials. *Lancet, 351*(9114), 1451-1467.
- Fallowfield, L. (2005). Acceptance of adjuvant therapy and quality of life issues. *Breast, 14*(6), 612-616.
- Fink, A.K., Gurwitz, J., Rakowski, W., Guadagnoli, E., & Silliman, R.A. (2004). Patient beliefs and tamoxifen discontinuance in older women with estrogen receptor-positive breast cancer. *Journal of Clinical Oncology, 22*(16), 3309-3315.
- Fisher, B., Costantino, J.P., Wickerham, D.L., Redmond, C.K., Kavanah, M., Cronin, W.M., et al. (1998). Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *Journal of the National Cancer Institute, 90*(18), 1371-1388.
- Fisher, B., Dignam, J., Bryant, J., DeCillis, A., Wickerham, D.L., Wolmark, N., et al. (1996). Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. *Journal of the National Cancer Institute, 88*(21), 1529-1542.
- Gilbert, J.R., Evans, C.E., Haynes, R.B., & Tugwell, P. (1980). Predicting compliance with a regimen of digoxin therapy in family practice. *Canadian Medical Association Journal, 123*(2), 119-122.
- Goss, P.E., Ingle, J.N., Martino, S., Robert, N.J., Muss, H.B., Piccart, M.J., et al. (2005). Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: Updated findings from NCIC CTG MA.17. *Journal of the National Cancer Institute, 97*(172), 1262-1271.
- Green, B.L., Rowland, J.H., Krupnick, J.L., Epstein, S.A., Stockton, P., Stern, N.M., et al. (1998). Prevalence of posttraumatic stress disorder in women with breast cancer. *Psychosomatics, 39*(2), 102-111.
- Grunfeld, E.A., Hunter, M.S., Sikka, P., & Mittal, S. (2005). Adherence beliefs among breast cancer patients taking tamoxifen. *Patient Education and Counseling, 59*(1), 97-102.
- Hartigan, K. (2003). Patient education: The cornerstone of successful oral chemotherapy treatment. *Clinical Journal of Oncology Nursing, 7*(6, Suppl.), 21-24.
- Haynes, R.B., McDonald, H.P., & Garg, A.X. (2002). Helping patients follow prescribed treatment: Clinical applications. *JAMA, 288*(22), 2880-2883.
- Haynes, R.B., Yao, X., Degani, A., Kripalani, S., Garg, A., McDonald, H.P. (2005). Interventions for enhancing medication adherence. *Cochrane Database of Systematic Reviews*, CD000011.
- Hill, J. (2005). Adherence with drug therapy in the rheumatic diseases. Part one: A review of adherence rates. *Musculoskeletal Care, 3*(2), 61-73.
- Howell, A., Cuzick, J., Baum, M., Buzdar, A., Dowsett, M., Forbes, J.F., et al. (2005). Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet, 365*(9453), 60-62.
- Jenkins, V., Fallowfield, L.J., & Poole, K. (2001). Are members of multidisciplinary teams in breast cancer aware of each other's informational roles? *Quality in Health Care, 10*(2), 70-75.
- Jenkins, V., Shilling, V., Deutsch, G., Bloomfield, D., Morris, R., Allan, S., et al. (2006). A 3-year prospective study of the effects of adjuvant treatments on cognition in women with early stage breast cancer. *British Journal of Cancer, 94*(6), 828-834.
- Jenkins, V., Shilling, V., Fallowfield, L., Howell, A., & Hutton, S.

- (2004). Does hormone therapy for the treatment of breast cancer have a detrimental effect on memory and cognition? A pilot study. *Psycho-Oncology*, 13(1), 61-66.
- Kirk, M., & Hudis, C. (2006, June). *Adherence to prescribed oral medications: Understanding the barriers to optimizing hormonal therapy in breast cancer (BC)*. Poster session presented at the American Society of Clinical Oncology 42nd Annual Meeting, Atlanta, GA.
- Lash, T.L., Fox, M.P., Westrup, J.L., Fink, A.K., & Silliman, R.A. (2006). Adherence to tamoxifen over the five-year course. *Breast Cancer Research and Treatment*, 99(2), 215-220.
- Lev, E.L. (1997). Bandura's theory of self-efficacy: Applications to oncology. *Scholarly Inquiry for Nursing Practice*, 11(1), 21-37.
- Liu, J.E., Mok, E., & Wong, T. (2006). Caring in nursing: Investigating the meaning of caring from the perspective of cancer patients in Beijing, China. *Journal of Clinical Nursing*, 15(2), 188-196.
- Long-Term Intervention With Pravastatin in Ischaemic Disease Study Group. (1998). Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *New England Journal of Medicine*, 339(19), 1349-1357.
- Martin, B., Barghout, V., & Hutchins, L. (2006). Compliance and persistence of tamoxifen and aromatase inhibitors in breast cancer patients [Abstract 179]. *European Journal of Cancer*, 42(4), 96.
- Maurice, A., Howell, A., Evans, D.G., O'Neil, A.C., & Scobie, S. (2006). Predicting compliance in a breast cancer prevention trial. *Breast Journal*, 12(5), 446-450.
- Morisky, D.E., Green, L.W., & Levine, D.M. (1986). Concurrent and predictive validity of a self-reported measure of medication adherence. *Medical Care*, 24(1), 67-74.
- Murthy, V., Bharia, G., & Sarin, R. (2002). Tamoxifen non-compliance: Does it matter? [Letter to the editor]. *Lancet Oncology*, 3(11), 654.
- Owusu, C., Buist, D., Field, T., Lash, T.L., Thwin, S., & Silliman, R. (2006). Tamoxifen discontinuance among women aged 65 years and older with estrogen receptor positive breast cancer [Abstract]. Proceedings of the 2006 ASCO annual meeting. *Journal of Clinical Oncology*, 24(18, Suppl.), 648.
- Palmer, S.C., Kagec, A., Coyne, J.C., & DeMichele, A. (2004). Experience of trauma, distress, and posttraumatic stress disorder among breast cancer patients. *Psychosomatic Medicine*, 66(2), 258-264.
- Partridge, A.H., LaFountain, A., Taylor, B.S., & Asnis-Alibozek, A. (2006, December). *Adherence with adjuvant anastrozole therapy among women with early-stage breast cancer*. Poster session presented at the 29th Annual San Antonio Breast Cancer Symposium, San Antonio, TX.
- Partridge, A.H., Wang, P.S., Winer, E.P., & Avorn, J. (2003). Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. *Journal of Clinical Oncology*, 21(4), 602-606.
- Powles, T., Eeles, R., Ashley, S., Easton, D., Chang, J., Dowsett, M., et al. (1998). Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial. *Lancet*, 352(9122), 98-101.
- Smith, D.L. (1989). Compliance packaging: A patient education tool. *American Pharmacy*, NS29(2), 42-53.
- Stephenson, B.J., Rowe, B.H., Haynes, R.B., Macharia, W.M., & Leon, G. (1993). The rational clinical examination: Is this patient taking the treatment as prescribed? *JAMA*, 269(21), 2779-2781.
- Stilley, C.S., Sereika, S., Muldoon, M.F., Ryan, C.M., & Dunbar-Jacob, J. (2004). Psychological and cognitive function: Predictors of adherence with cholesterol lowering treatment. *Annals of Behavioral Medicine*, 27(2), 117-124.
- Turner, P., & Williams, C. (2002). Informed consent: Patients listen and read, but what information do they retain? *New Zealand Medical Journal*, 115(1164), U218.
- United Kingdom Prospective Diabetes Study Group. (1995). 13: Relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. *BMJ*, 310(6972), 83-88.
- Waterhouse, D.M., Calzone, K.A., Mele, C., & Brenner, D.E. (1993). Adherence to oral tamoxifen: A comparison of patient self-report, pill counts, and microelectronic monitoring. *Journal of Clinical Oncology*, 11(6), 1189-1197.
- Wroth, T.H., & Pathman, D.E. (2006). Primary medication adherence in a rural population: The role of the patient-physician relationship and satisfaction with care. *Journal of the American Board of Family Medicine*, 19(5), 478-486.
- Yen, T.W., Hunt, K.K., Mirza, N.Q., Thomas, E.S., Singletary, S.E., Babiera, G.V., et al. (2004). Physician recommendations regarding tamoxifen and patient utilization of tamoxifen after surgery for ductal carcinoma in situ. *Cancer*, 100(5), 942-949.

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