5-2011

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Acknowledgements: The Michigan Nurse Corp Fellowship and Oncology Nursing Society.

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KEY WORDS: Cancer**,** Oral Agents, Antineoplastic, Adherence, Scope of problems

Abstract

OBJECTIVE: Given the increasing use of oral antineoplastic agents in cancer management, patient adherence is critical to successful treatment outcomes. This article reviews the scope of the problem and issues of adherence to oral antineoplastic agents.

DATA SOURCES: Research based and other articles, newsletters, and conference presentations.

CONCLUSION: Suboptimal adherence to oral antineoplastic agents is a significant clinical problem that may result in disease or treatment complications, adjustment in treatment regimen, disease progression, and premature death.

IMPLICATIONS FOR NURSING PRACTICE: Healthcare providers need to monitor and facilitate adherence by identifying barriers and implementing strategies to assure adherence, and therefore, improve clinical outcomes.

Recent progress in the treatment of cancer has seen an accelerated use of oral antineoplastic agents. At this time, nearly 50 oral antineoplastic agents are approved for use in the United States alone, with nearly half of all new agents in development being oral.[1,2] This new treatment paradigm shifts delivery of intravenous chemotherapy from a safe, controlled process monitored on a regular basis by oncologists and oncology nurses in hospitals or outpatient clinics to patients' homes where the complexity of knowing dosing, side effects, and toxicities becomes the patient and family responsibility. The dosing regimens are often complex, and even for the most medically sophisticated patient and family, responsibilities for monitoring and taking medications, and then managing symptoms, side effects, and adverse events can be overwhelming.[2] The problem is especially grave for cancer patients who often require long-term or lifelong therapy, because poor medication adherence leads to unnecessary disease progression, disease complications, reduced functional abilities, a lower quality of life, and premature death.[3] In this article, the problem, scope, and issues involved with adherence to oral antineoplastic agents are discussed.

The Definition of Adherence

There is no "gold standard" definition of adherence. However, there is a vast literature examining medication adherence, most of which offer definitions.

Conceptual Definition of the Health Status Outcome Adherence

The World Health Organization defines adherence as the extent to which a person's behavior corresponds with agreed recommendations from a health care professional.[4] A commonly used definition is the extent to which a person's behavior-taking medications, following a diet and/or exercising follows recommendations from a healthcare provider.[5] A more precise definition of medication adherence was recently offered by the International Society for Pharmacoeconomics and Outcome Research (ISPOR), 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." ISPOR extends this definition by adding persistence, which they define as "the duration of time from the initiation of the medication to discontinuation of therapy".[6] Each of these conceptual definitions lay the foundation for measuring adherence**.**

Operational Definition of the Health Status Outcome Adherence

Medication adherence is routinely operationalized in the literature as a percentage of how many of the prescribed pills a patient has taken (i.e., 80%, 90%, or 100%) compared to what they were prescribed. In many instances in the literature, a patient is considered to be adherent when they have taken 80% of a prescribed medication.[7] Often, when self-report of medication adherence is used as the measure, a yes or no (dichotomous) question is asked of the patient.[8,9] When Medication Event Monitoring System (MEMS [electronic pill boxes that alarm and measure cap openings]) are used, the number of bottle cap openings are compared to the number of expected bottle cap openings that are prescribed during a treatment period.[10] When pharmacy claims data are used to examine adherence, a proportion of the days that the patient had the medication available is compared to the proportion of the days that the patient had the medication prescribed over the observation period and is calculated as the percentage of adherence.[11] When biologic measures, such as urine or serum assays are used, specific ranges of blood or urine levels are expected to be associated with adherence to a medication regimen.[12,13] The operational definition of adherence is dependent upon which of these measures, or combination of these measures, is used to assess adherence.

Definition of adherence used in research on oral agents. Three systematic reviews have been conducted on oral antineoplastic agents. One review of 12 studies used the most commonly cited definition of adherence in the literature, 'the extent to which a person's behavior coincides with medical or health advice',[14] a second review (n = 22) used the ISPOR definition,[15] while the third (n = 6) concluded that no standard definition of adherence was used across studies and this made comparison of results between studies difficult.[16] Of the 43 studies in the literature, only 24 reported a definition of adherence (See article on assessment and measurement elsewhere in this issue). Examples of general definitions were 90%-100% of pills taken and/or the extent to which a person's behavior coincides with medical or health advice. Specific definitions included 100% adherence for taking mediation at correct date or time, or the prescribed number of doses taken based on pill count and MEMS, within 2-hours of

prescribed dosing interval and with the correct number on day of treatment.[17] Definitions of adherence are more precise and measurable in the more recent oral antineoplastic agent studies.

The definition to be used in this issue of Seminars in Oncology in Oncology Nursing is that offered by ISPOR and is the "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 of the medication to discontinuation of therapy". The ISPOR definition encompasses the complexity of dosing regimens for oral antineoplastic agents.

Frameworks Used to Examine Medication Adherence

Problems with medication adherence include patient factors, disease factors, and system factors. Patient factors can include age, education, income, cognition, attitude, beliefs, expectations, perception of illness, the environment, or health literacy. Influencing disease factors can include number of comorbid conditions, severity of disease, severity of outcome, and response to treatment. System factors may include the organizational structure of the healthcare system, the relationship with provider, and distance to health services.[18] The Health Belief Model, often used to study adherence, focuses on the individual's evaluation of his or her own health condition (disease severity and perceived vulnerability to the disease state), risks and benefits of adherence to the medication, and "cues to action" that prompt taking the medication.[19] Piette and colleagues[18,20] examined regimen complexity, sociodemographic characteristics such as living alone and distance from children, disease characteristics and comorbidities, and trust with clinicians that influence medication adherence. Dunbar-Jacob and colleagues[21-23] examine the sociodemographic (age, education, marital status, ethnicity, income, and insurance), psychosocial (depression, personality traits, optimism, and emotion expressiveness), health status (smoking status, body mass index, physical activity, and cancer or heart disease), and procedural factors (pill type, changes in pills, and clinic site). Given and colleagues[24] used a cognitive behavioral model in an educational approach to symptom management coupled with reminders to take medications in a trial on oral antineoplastic agent adherence. To a great extent, the literature on oral antineoplastic agent adherence does not include a framework. This has limited understanding of the factors that may influence adherence.

Factors That Affect Adherence

A large body of empirical evidence exists on factors contributing to medication adherence in general, as investigators have tried to identify predictors of nonadherence to develop interventions. However, the relationship between these factors and adherence have been inconsistent; and most studies have found weak associations (< 0.15 r) with nonadherence.[25,26] No simple explanation for nonadherence exists. Nonetheless, the following are the patient, disease, and system factors found in the literature associated with nonadherence (See Table 1).

Patient Factors

Sociodemographics. Age, race, education, and income level seem to influence adherence. However, the role of age in predicting adherence is unclear with some arguing elderly have routines which lead to better adherence,[27] while others have found errors of omission and nonadherence.[28,29] Middle age adults are known to make more adherence errors than the elderly.[27-29] In breast cancer patients taking long-term tamoxifen, younger women are more adherent.[7,30,31] In some instances, males, non Caucasians, those who have less than a high school education, and are low-income have been found to be less adherent.[32-34]

Depression. In general, studies relate depression with lower adherence.[35,36] In some instances, anxiety seems to contribute to nonadherence.[37,] In cancer patients, increased depressive symptoms are associated with nonadherence.[31,33,38] The mechanism by which symptoms impact adherence remains unclear and likely complex, yet when identified could ultimately be a modifiable risk factor.[39] Scientists theorize that increased levels of depression may decrease the capability to be adherent.

Beliefs about treatment and outcome expectation. There is some evidence that adherence correlates with a patient's belief in the severity of the disease to be prevented or treated,[23,40,41] thus one would expect all cancer patients to adhere. Patient perceptions about their illness strongly influenced adherence in cancer patients, consequently affecting the patients' motivation, and ultimately, the ability of the oral antineoplastic agents to effectively manage the disease.[14] For example, in breast cancer patients

taking Tamoxifen, the belief that nothing was to be gained by taking the oral antineoplastic agent was the predominant determinant of adherence.[9,42]

Health literacy. Approximately 25% of the US population is illiterate.[43] Even patients who can read and understand simple materials may be unable to comprehend more complicated written information about their disease and medications to treat it. Health literacy is the ability to read, understand, and act on health information. Poor skills lead to medications error, and impair the ability to remember and follow treatment recommendations and reduce effective interaction with providers.

Social support environment. Family members, friends, and caregivers are an important component of the social environment and they can provide reminders to take the medication or administer the medication when necessary. Social support has been associated with good medication adherence.[44]

Disease Factors

Disease type. Literature on poor adherence to oral medications can be found for many types of diseases. This includes antihyperglycemics for diabetes (28.9%),[45] lipid lowering drugs for coronary artery disease (8% to 40.6%),[46,47] statins for acute coronary syndromes (20.0% to 40.1%),[48,49] antipsychotic drugs for psychosis (21.2%),[50] protease inhibitor therapy for HIV (41.0%),[51] and immunomodulatory drugs for multiple sclerosis (27.0%).[52] As stated earlier, adherence for cancer patients ranged from 16% to 100% and these findings will be discussed further in the article on measurement elsewhere in this issue.

Disease stage. Often, oral antineoplastic agents are prescribed for patients in later stages of disease as a last resort after other types of treatment have failed.[24] However, gefitinib recently improved survival among metastatic lung cancer patients as a first drug line in a phase III trial.[53] Clinicians have reported using erlotinib for first line treatment in a small subset of advanced unresectable lung cancer patients who have a particular gene mutation.[54]

Side effects of disease or treatment. The frequency, severity, and type of side effects of the medications or the disease may also affect adherence. Studies of chronic disease indicate that patients decrease adherence as symptoms and side effects occur.[9,35,55-58] Side effects from the disease and/or the

treatment of cancer may also affects adherence.[9,33] Given and colleagues[24] recently conducted an intervention study finding symptom management improved adherence. It is probable that when patients perceive symptoms to be associated with oral agents, they are more likely to modulate adherence to self-manage symptoms.

Complexity of the dosing regimen. A large meta-analysis of 76 studies demonstrated that adherence is adversely proportional to medication-taking frequency.[59] Decreasing the frequency of the dose is known to improve both symptom control and adherence.[60] Oral agents are often administered on different dosing schedules and the complexity of the regimen may have an effect on adherence.[9,61-63] As noted earlier in the Given[24] study, as the complexity of the dosing regimen increased, adherence decreased. Examples of complex regimens include the 14 days on, 7 days off, medication cycle or the 7 days on, 7 days off, medication cycle.

Polypharmacy and drug interactions. One study on polypharmacy with oncology pharmacists identified 12 clinically significant potential drug-to-drug interactions with oral antineoplastic agents and commonly used medications.[64] Drug-to-drug interactions can lead to adverse clinical outcomes, particularly in oncology, because of the narrow antineoplastic index of oral agents and a high risk of additional medications prescribed for age-related organ dysfunction.[65,66] Not all drug—drug interactions can be predicted, and those that are predictable are not always avoidable. However, increased awareness of the potential for these interactions will allow healthcare providers to minimize the risk by choosing appropriate drugs and by monitoring for signs of interaction.[66]

System Factors

Relationship and communication with healthcare provider. Clinicians generally assume that patients are taking drugs as prescribed, and if a clinician discusses the topic with their patient, they believe patients when they say they are adherent.[14] Specific clinician practices, continuity of care, and convenience of the office setting,[67,68] and the relationship between the patient and the health care provider[14,69] have had weak to moderate associations with adherence. When clinicians are aware of potential adherence problems, they have been unable to predict which patients may be nonadherent.[70,71] A

systematic review of the research on communication between patients and healthcare providers about medications found that when physicians tended to dominate discussions, patient adherence decreased.[72,73]

Out-of-pocket costs. Out-of-pocket costs for medications have been found to be a risk factor for nonadherence.[18,20] In oncology, large out-of-pocket costs of oral agents[62,74,75] have influenced adherence. Although a person might believe that he is fully capable of following a prescribed treatment regimen, he may not adhere to therapy if he does not believe that his cost-benefit balance favors adherence.[14] So, for cancer patients, if out-of-pocket costs are significant, adherence may be more difficult. Medications delivered orally may be more costly than those by infusion, as insurance is more likely to cover infusions that are given in a hospital or clinic as opposed to at home

In summary, there are many factors that may influence adherence. However, most studies have found weak associations. Clinicians need to be aware of factors that may influence adherence when developing strategies to reduce nonadherence.

The Benefits and Disadvantages of Oral Antineoplastic Agents

Several emerging trends in use of oral antineoplasticts are listed in Table 2. Despite difficulties with adherence, oral antineoplastic agents provide a potentially enhanced mode of cancer control by sustaining drug levels and prolonging continuous drug exposure to cancerous cells. The continual suppression of cancer cell growth prevents disease progression. Other advantages of oral antineoplastic agents include patient benefits, such as minimal disruption in work life, eliminating transportation issues, reducing the overall visits to the clinic or doctor's office, and eliminating the need for intravenous access. Some patients prefer oral antineoplastic agents because they are perceived as less toxic and will choose them over I.V. agents when the two therapies are considered equally effective.[76] However, other patients consider it a less "serious" form of therapy, and feel that I.V. therapy is needed for maximum benefit. One of the major drawbacks of oral antineoplastic agent is that there is less opportunity for healthcare professionals to interact with patients, assess disease response and toxicity, and to provide symptom management guidance or education to patients.

Antineoplastic Index for Oral Cancer Treatments.

Molecularly targeted oral antineoplastic agents are highly selective for molecules that establish and maintain malignant cell expression, thus, the major reason for increased emphasis on adherence to oral cancer therapies. For example, imatinib and erlotinib, are different from traditional chemotherapy because they inhibit or turn off enzymes active in cancer progression. Success rates with imatinib are high, but to achieve—and maintain—these results, long-term administration is required in responsive patients.[77] Pharmacokinetic literature suggests a narrow antineoplastic index for oral cancer agents,[78] thus increasing the importance of adherence. Oral antineoplastic agents may be used as the sole treatment regimen, as with capecitabine[79] in combination with other oral agents, or with intravenous chemotherapy treatment. What is not known is what level of adherence is required to achieve an antineoplastic dose when using oral agents under each of these treatment approaches. For example, the antineoplastic benefit derived from agents with longer half-lives may be minimally compromised by missed doses.[80,81] Some studies have included assessments of adherence to limit this type of error.[82] However, adherence in a clinical trial tends to be much higher than what is observed in clinical practice.[15] Furthermore, rates of adherence with oral medication in clinical studies are likely to be inflated over what would be observed outside of a trial because of the careful selection of patients for recruitment and the intense attention that is paid to them once they are enrolled.[14,71] In the community cancer setting, adherence is thought to be more challenging.

Safe Handling of Antineoplastic Agents

Recent discussions have highlighted the need for safe handling of potentially hazardous drugs, such as the antineoplastics. The American Society of Clinical Oncology and Oncology Nursing Society have established chemotherapy administration safety standards for the clinical setting.[83] These procedures need to be implemented in the home setting to assure the patient and family members are safe.

Adherence, an Unrecognized Problem

In general, a review of 50 years of research across diseases found an overall nonadherence rate of 24.5%, with minimal difference found in adherence for medications taken for prevention or treatment.[84]

Furthermore, adherence has been directly linked to effectiveness of medical treatment.[68] The most common reasons for nonadherence are: not filling a prescription, incorrect dosing, altering medication times, forgetting, or stopping before advised.[85,86] Problems with adherence are thought to be unintentional and are attributed to the patient's forgetfulness, difficulty with adapting to changes in the daily routine, or being asymptomatic.[34] However, patients may choose not to fill a script if they believe it will be ineffective or if the cost is prohibitive or they have no means of reaching a pharmacy.[87] Evidence demonstrates that adherence to treatment regimens that are documented to reduce mortality or the risk of other catastrophic outcomes (e.g., death) is poor.[88,89]

Adherence to Oral Antineoplastic Agents

In oncology, cancer patients are thought to be highly motivated by the gravity of their disease, with "too much to lose" by being nonadherent ,as the majority of these patients are often in the late stage of their disease when other therapy has failed.[90] However, some patients experience confusion due to the complexity of the regimen, or may simply forget to take their medication, self-modulate their doses, or not obtain a prescription.[24]

Adherence Rates in Oral Antineoplastic Agents. Systematic reviews of antineoplastic agent studies (n = 22) found adherence ranged between 16% and 100%.[14-16] What is not clear in many of these studies is if under dosing or over dosing led to the nonadherence. Given and colleagues[24,91] conducted an intervention trial (n = 119) finding adherence was 88% (n = 50 of 57) for patients with a 28 day medication cycle, 36% (n=9 of 25) for patients with a 14 days on, 7 days off medication cycle, and 33% (n = 3 of 9) with a 7 days on, 7 days off medication cycle (full adherence was defined as 78% of medication taken).The low adherence rate found in these studies may compromise the therapeutic index needed when administering oral antineoplastic agents.

Over Adherence in Oral Antineoplastic Agent Studies. Over adherence is also a problem. Over adherence was found at a rate of 48% (n = 12 of 25) for patients with 14 days on, 7 days off medication cycle, and at a rate of 67% (n = 6 of 9) with 7 days on, 7 days off medication cycle.[24,91] In a randomized control drug trial with adherence as a secondary endpoint, researchers found over adherence: days of

taking medications beyond the end of an expected cycle; taking extra doses in one day; and missing a day and compensating with a double dose the next day.[92] The high rate of over adherence found may cause toxicity or lead to adverse events.

Adherence Persistence Rates in Non-hormonal therapy. Studies of persistence, or the duration of time from the initiation to the discontinuation of therapy, among oral antineoplastic agents are rare. However, insights can be learned from the long-term studies of tamoxifen use in breast cancer patients. Adherence rates from long-term studies of breast cancer patients prescribed tamoxifen following the end of chemotherapy found that rates declined over time, 17% in year 1, 19% to 28% in year 2, 21% to 38% in year 3, and 50% by year 4 of treatment.[7,11,30,31,42,] Therefore, in a regimen that takes place over prolonged time, adherence declines drastically.

Reasons for Nonadherence . Three of the studies on oral antineoplastics collected information on patient-reported reasons for nonadherence. These reasons included reports of carelessness about taking medications (80%),[93] forgetting to take medication (30% to 60%),[91,93] purposely skipped doses (35%),[94] late dosing (26.7%),[94] concerns over side effects (16.6%)[94] and 20% not understanding written materials about the prescription.[94] One study also found the complexity of the regimen drastically reduced adherence.[24] These studies provide a general understanding of reasons for nonadherence, and point out the need for patients to have reminders when taking oral antineoplastic agents.

The Consequence of Nonadherence to Oral Antineoplastic Agents

Suboptimal adherence to oral therapies can have multiple consequences. Poor adherence can severely impede the efficacy of oral regimens.[61] Poor adherence can lead to compromised healthcare provider communication, side effects and/or adverse events due to toxicities, increased use of healthcare resources, and decreased survival.

Poor Healthcare Provider Communication

Suboptimal adherence can compromise the patient-provider relationship, as misconceptions about the effects of a therapy may lead to a breakdown in communication and negatively affect a patient's view of care.[90] The disconnect between what dose the patient receives and the clinician's assumption that

the patient is taking the dose as prescribed, may result in the clinician changing the dose or agent due to a belief that the patient is non-responsive to the treatment or having unexpected side effects.[2,74]

Ineffective Antineoplastic Agents

As stated previously, when less than a therapeutic dose of an antineoplastic agent is taken, severe consequences may occur. This includes complications due to treatment or disease with reduced functional abilities and a lower quality of life, and in some instances, unnecessary disease progression and premature death.[3]

Side effects, adverse effects, and toxicities. Patients who over-adhere, especially those who take doses more frequently than prescribed, or at the wrong time of day, may experience greater levels of toxicities.[15] Consequently, side effects and adverse events may be more likely in patients who are nonadherent.

Poorer survival. In general, an association has been found between medication adherence and mortality.[95] For example, participants in the Beta Blocker Heart Attack Trial who took 75% or less of prescribed medications were 2.5 times more likely to die than were those who were adherent to treatment.[96,97] This may also be true with oral antineoplastic agents.

Increased Use of Healthcare Resources.

Nonadherence in a variety of patient populations has been associated with increased use of health care resources, including more physician visits, higher hospitalization rates, and longer stays.[26,88] Lack of adherence to oral chemotherapy can contribute to variability in a drug's antineoplastic agent effect if a clinician incorrectly attributes the patient's worsening condition to an absence of drug activity and may lead to unnecessary testing and hospitalization.[31]

Strategies to Improve Adherence

Mixed results have been reported for interventions to improve medication adherence in general[91] Effective strategies are multidisciplinary and multimodal.[98,99] However, a recent systematic review of interventions to enhance patient adherence to medications concluded current methods are complex, labor-intensive, and not predictably effective, therefore, not able to be used in the clinical setting.[100] Simple pill

reminders such as plastic pill boxes and calendars have demonstrated effectiveness in some types of medication adherence studies, however limited evidence is available when the complexity of the regimen with oral antineoplastic agents and further study is needed. These findings will be discussed in detail in the article on interventions, providing guidance for practitioners.

The Multiple Challenges to Oral Antineoplastic Agent Adherence

Multiple challenges to oral antineoplastic agent adherence exist in research and clinical practice. The limited available evidence suggests that adherence to oral agents is a significant clinical problem and may have a substantial impact on the antineoplastic agent success or failure of oral regimens for the prevention or treatment of malignancies. Patient adherence to antineoplastic regimens will be increasingly important to oncology as additional oral treatments are adopted for use in cancer care.[15]

In research, there is no 'gold' standard definition for adherence, to allow for comparison across studies. Additionally, effective measurement methods of adherence are difficult to implement and track the medication regimen to identify if the patient is adherent or nonadherent. Measuring and studying adherence to oral antineoplastic agents is difficult because patients are aware of being observed and patients may adhere more than the average patient who is receiving the same therapy.[15] Systematic assessment of adherence should be included in phase III trials, as well as off-study treatment with oral antineoplastic agents. Future research needs to develop better methods for measurement and intervention. Poor adherence to medication is an ever-present and complex problem potentially contributing to substantial worsening of disease control,[101,102] altering the outcome of treatment.[14]

In clinical practice there is a need to better understand how patients' determinants influence adherence and consequently develop interventions to assist patients to adhere to oral antineoplastic. Suboptimal adherence may adversely impact the efficacy and toxicity of oral therapeutic agents. Although the impact of nonadherence may differ between clinical care and research, and both are important.

TABLE 1.
Barriers to Optimal Adherence

Patient factors
Sociodemographic
Depression
Beliefs about treatment and outcome expectation
Health literacy
Social support
Disease factors
Disease type
Disease stage
Side effects of disease or treatment
Complexity of the dosing regimen
Polypharmacy and drug interactions
System factors
Relationship and communication with healthcare provider
Out-of-pocket costs

TABLE 2.
Emerging Trends in Cancer Care

Increasing use of oral therapies
Molecularly targeted therapies with attenuated side effects versus traditional chemotherapy
Considering cancer a chronic disease with new emphasis on ongoing therapy
Longer survival times requiring long-term daily medication
Changing needs for patients and caregivers to monitor/ manage side effects, toxicities, and adverse events
Increased patient responsibility for adherence to treatment

References

1. Moore S, Stoker Y. Promoting patient adherence to oral cancer treatment. *Oncol Nurs Forum*. 2008;35(3):501-501.
2. Weingart SN, Bach PB, Johnson SA, et al. NCCN Task Force Report: oral chemotherapy. *J Natl Compr Canc Netw.* 2008;6(suppl 3):S-1-S-17.
3. World Health Organization. *Adherence to long-term therapies: evidence for action*. Geneva, Switzerland; 2003. http://www.who.int/chp/knowledge/publications/adherence_full_report.pdf Accessed July 11, 2010.
4. World Health Organization. Definitions [Web page]. 2008. http://www.who.int/hac/about/definitions/en/. Accessed July 8, 2010.
5. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. *Cochrane Database of Systematic Reviews* 2008, Issue 2. Art. No: CD000011.
6. Cramer JA, Roy A, Burrell RA, et al. Medication compliance and persistence: terminology and definitions. *Value Health*. 2008;11(1):44-47.
7. Partridge AH, Wang PS, Winer EP, Avorn J. Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. *J Clin Oncol.* 2003;21(4):602-606.
8. Sadahiro S, Ohki S, Yamaguchi S, et al. Feasibility of a novel weekday-on/weekend-off oral UFT schedule as postoperative adjuvant chemotherapy for colorectal cancer. UFT Compliance Study Group, Kanagawa, Japan. *Cancer Chemother Pharmacol.* 2000;46(3):180-184.
9. Grunfeld EA, Hunter MS, Sikka P, Mittal S. Adherence beliefs among breast cancer patients taking tamoxifen. *Patient Educ Couns.* 2005;59(1):97-102.
10. Buckwalter KC, Wakefield BJ, Hanna B, Lehmann J. New technology for medication adherence: electronically managed medication dispensing system. *J Gerontol Nurs*. 2004;30(7):5-8.
11. Partridge AH, LaFountain A, Mayer E, Taylor BS, Winer E, Asnis-Alibozek A. Adherence to initial adjuvant anastrozole therapy among women with early-stage breast cancer. *J Clin Oncol.* 2008;26(4):556-562.

12. Levine AM, Richardson JL, Marks G, et al. Compliance with oral drug therapy in patients with hematologic malignancy. J Clin Oncol. 1987;5(9):1469-1476.

13. Traore F, O'Riordan M, Myers C, et al. How low is too low? Use of cluster analysis to define low levels of mercaptopurine metabolites. *Pediatr Blood Cancer.* 2006;46(2):187-192.

14. Partridge AH, Avorn J, Wang XS, Winer EP. Adherence to therapy with oral antineoplastic agents. *J Natl Cancer Inst.* 2002;94(6):652-661.

15. Ruddy K, Mayer E, Partridge A. Patient adherence and persistence with oral anticancer treatment. CA Cancer J Clin. 2009;59(1):56-66.

16. Escalada P, Griffiths P. Do people with cancer comply with oral chemotherapy treatments? *Br J Community Nurs.* 2006;11(12):532-536.

17. Klein CE, Kastrissios H, Miller AA, et al. Pharmacokinetics, pharmacodynamics and adherence to topotecan in myelodysplastic syndromes: a cancer and leukemia group B study. Cancer Chemother Pharmacol. 2006;57(2):199-206.

18. Piette JD, Heisler M, Wagner TH. Medication characteristics beyond cost alone influence decisions to underuse pharmacotherapy in response to financial pressures. *J Clin Epidemiol.* 2006;59(7):739-746.

19. Becker MH, Radius SM, Rosenstock IM, Drachman RH, Schuberth KC, Teets KC. Compliance with a medical regimen for asthma: a test of the health belief model. *Public Health Rep.* 1978(93):268-277.

20. Piette JD, Heisler M, Krein S, Kerr EA. The role of patient-physician trust in moderating medication nonadherence due to cost pressures. Arch Intern Med. 2005;165(15):1749-1755.

21. Brunner R, Dunbar-Jacob J, Leboff MS, et al. Predictors of adherence in the Women's Health Initiative Calcium and Vitamin D Trial. *Behav Med.* 2009;34(4):145-155.

22. Stilley CS, Bender CM, Dunbar-Jacob J, Sereika S, Ryan CM. The impact of cognitive function on medication management: three studies. *Health Psychol.* 2010;29(1):50-55.

23. Chia L, Schlenk EA, Dunbar-Jacob J. Effect of personal and cultural beliefs on medication adherence in the elderly. *Drugs Aging.* 2006;23(3):191-202.

24. Spoelstra S, Given BA, Given CW, Ahn SZ. (2011). Interventions to improve adherence and symptoms for oral agents. Paper presented at: 11th National Conference on Cancer Nursing Research, February 10-12, 2011; Los Angeles, CA.

25. Choudhry NK, Setoguchi S, Levin R, Winkelmayer WC, Shrank WH. Trends in adherence to secondary prevention medications in elderly post-myocardial infarction patients. *Pharmacoepidemil Drug Saf*. 2008;17(12):1189-1196.

26. Chan DC, Shrank WH, Cutler D, et al. Patient, physician, and payment predictors of statin adherence. *Med Care.* 2010;48(3):196-202.

27. Park DC, Shaw RJ. Effect of environmental support on implicit and explicit memory in younger and older adults. *Psychol Aging*. 1992;7(4):632-642.

28. Brown SC, Park DC. Theoretical models of cognitive aging and implications for translational research in medicine. *Gerontologist*. 2003;43(spec no 1):57-67.

29. Morrell RW, Park DC, Kidder DP, Martin M. Adherence to antihypertensive medications across the life span. *Gerontologist.* 1997;37(5):609-619.

30. Atkins L, Fallowfield L. Intentional and non-intentional non-adherence to medication amongst breast cancer patients. *Eur J Cancer*. 2006;42(14):2271-2276.

31. Barron TI, Connolly R, Bennett K, Feely J, Kennedy MJ. Early discontinuation of tamoxifen: a lesson for oncologists. *Cancer*. 2007;109(5):832-839.

32. Stephenson BJ, Rowe BH, Haynes RB, Macharia WM, Leon G. The rational clinical examination: Is this patient taking the treatment prescribed? *JAMA*. 1993;269(21):2779-2781.

33. Lebovits A, Strain JJ, Schleifer SJ, Tanaka JS, Bhardwaj S, Meese MR. Patient noncompliance with self-administered chemotherapy. *Cancer*. 1990;65(1):17-22.

34. Conn VS, Hafdahl AR, Cooper PS, Ruppar TM, Mehr DR, Russell CL. Interventions to improve medication adherence among older adults: meta-analysis of adherence outcomes among randomized controlled trials. *Gerontologist*. 2009;49(4):447-462.

35. Schlenk EA, Dunbar-Jacob J, Engberg S. Medication non-adherence among older adults: a review of strategies and interventions for improvement. *J Gerontol Nurs*. 2004;30(7):33-43.

36. Stilley CS, Sereika S, Muldoon MF, Ryan CM, Dunbar-Jacob J. Psychological and cognitive function: predictors of adherence with cholesterol lowering treatment. *Ann Behav Med.* 2004;27(2):117-24.

37. De Greest S, von Renteln-Kruse W, Steenman E, Degraeve S, Abraham IL. Compliance issues with the geriatric population: complexity with aging. *Nurs Clin North Am.* 1998;33(3):467-480.

38. Richardson JL, Shelton DR, Krailo M, Levine AM. The effect of compliance with treatment on survival among patients with hematologic malignancies. *J Clin Oncol*. 1990;8(2):356-364.

39. Wang PS, Bohn RL, Knight E, Glynn RJ, Mogun H, Avorn J. Noncompliance with antihypertensive medications: the impact of depressive symptoms and psychosocial factors. *J Gen Intern Med*. 2002;17(7):504-511.

40. DiMatteo MR, Haskard KB, Williams SL. Health beliefs, disease severity, and patient adherence: A meta-analysis. *Med Care.* 2007;45(6):521-528.

41. Fogarty L, Roter D, Larson S, Burke J, Gillespie J, Levy R. Patient adherence to HIV medication regimens: a review of published and abstract reports. *Patient Educ Couns.* 2002;46(2):93-108.

42. Fink AK, Gurwitz J, Rakowski W, Guadagnoli E, Silliman RA. Patient beliefs and tamoxifen discontinuance in older women with estrogen receptor-positive breast cancer. *J Clin Oncol*. 2004;22(16):3309-3315.

43. Lasater L, Mehler PS. The illiterate patient: screening and management. *Hosp Pract.* 1998;33(4):163-165, 169-170.

44. Ammassari A, Trotta MP, Murri R, et al. Correlates and predictors of adherence to highly active antiretroviral therapy: overview of published literature. *J Acquir Immune Defic Syndr.* 2002;31(suppl 3):123-127.

45. Lau DT, Nau DP. Oral antihypergylcemic medication nonadherence and subsequent hospitalization among individuals with Type 2 diabetes. *Diabetes Care*. 2004;27(9):2149-2153.

46. Di Martino M, Esposti LD, Ruffo P, et al. Underuse of lipid lowering drugs and factors associated with poor adherence: a real practice analysis in Italy. *Eur J Clin Pharmacol.* 2005;61(3):225-230.

47. Eagle KA, Kline-Rogers E, Goodman SG, et al. Adherence to evidence-based therapies after discharge for acute coronary syndromes: an ongoing prospective, observational study. *Am J Med.* 2004;117(2):73-81.

48. Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *JAMA*. 2002;288(4):462-467.

49. Benner JS, Glynn RJ, Mogun H, Neumann PJ, Weinstein MC, Avorn J. Long-term persistence in use of statin therapy in elderly patients. *JAMA*. 2002;288(4):455-461.

50. Knapp M, King D, Pugner K, Lapuerta P. Non-adherence to antipsychotic medication regimens: associations with resource use and costs. *Br J Psychiatry*. 2004;184:509-516.

51. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Inter Med.* 2000;133(1):21-30.

52. Tremlett H, Van der Mei I, Pittas F, et al. Adherence to the immunomodulatory drugs for multiple sclerosis: contrasting factors affect stopping drug and missing doses. *Pharmacoepidemiol Drug Saf.* 2008;17(6):565-576.

53. National Cancer Institute. *Gefitinib improves progression-free survival for metastatic lung cancers with EGFR mutations*. Washington, DC: National Health Institute; http://www.cancer.gov/clinicaltrials/results/gefitinib-NSCLC0810. Accessed August 24, 2010.

54. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med.* 2010;362(25):2380-2388.

55. Dunbar-Jacob J, Mortimer-Stephens MK. Treatment adherence in chronic disease. *J Clin Epidemiol.* 2001;54(suppl 1):S57-S60.

56. National Comprehensive Cancer Network. *The Complete Library of NCCN Clinical Practice Guidelines in Oncology*. 2006. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed July 29, 2010.

57. Korsch BM, Fine RN, Negrete VF. Noncompliance in children with renal transplants. *Pediatrics*. 1978;61(6):872-6.

58. Brown C, Battista DR, Sereika SM, Bruehlman RD, Dunbar-Jacob J, Thase ME. How can you improve antidepressant adherence? *J Fam Pract.* 2007;56(5):356-363.

59. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther*. 2001;23(8):1296-1310.

60. Richter A, Anton SF, Koch P, Dennett SL. The impact of reducing dose frequency on health outcomes. *Clin Ther*. 2003;25(8):2307-2335.

61. Bedell CH. A changing paradigm for cancer treatment: the advent of new oral chemotherapy agents. *Clin J Oncol Nurs.* 2003;7(suppl 6):5-9.

62. Hollywood E, Semple D. Nursing strategies for patients on oral chemotherapy. *Oncology (Williston Park)*. 2001;15(1 suppl 2):37-39, disc 40.

63. Aisner J. Overview of the changing paradigm in cancer treatment: oral chemotherapy. *Am J Health Syst Pharm.* 2007;64(9 supplement 5):S4-S7.

64. Chan A, Tan SH, Wong CM, Yap KY, Ko Y. Clinically significant drug-drug interactions between oral anticancer agents and nonanticancer agents: a Delphi survey of oncology pharmacists. *Clin Ther*. 2009;31(pt 2):2379-2386.

65. Lichtman SM, Boparai MK. Anticancer drug therapy in the older cancer patient: pharmacology and polypharmacy. *Curr Treat Options Oncol.* 2008;9(2-3):191-203.

66. Blower P, De Wit R, Goodin S, Aapro M. Drug-drug interactions in oncology: why are they so important and can they be minimized? *Crit Rev Oncol Hemato*l. 2005;55(2):117-142.

67. Sackett DL, Rosenberg WMC, Gray JAM, Haynes RB, Richardson WD. Evidence based medicine: what it is and what it isn't. *BMJ*. 1996;312(7023):71-72

68. DiMatteo MR, Giordani PJ, Lepper HS, Croghan TW. Patient adherence and medical treatment outcomes: a meta-analysis. *Med Care*. 2002;40(9):794-811.

69. Stewart M, Brown JB, Boon H, Galajda J, Meredith L, Sangster M. Evidence on patient-doctor communication. *Cancer Prev Control.* 1999;3(1):25-30.

70. van Dulmen S, Sluijs E, van Dijk L, de Ridder D, Heerdink R, Bensing J. Patient adherence to medical treatment: a review of reviews. *BMS Health Serv Res.* 2007;7:55.

71. Osterberg L, Blascheke T. Adherence to medication. *N Engl J Med*. 2005;353(5):487-498.

72. Stevenson FA, Cox K, Britten N, Dundar Y. A systematic review of the research on communication between patients and health care professionals about medicines: the consequences for concordance. *Health Expect.* 2004;7(3):235-245.

73. Bartel SB. Safe practices and financial considerations in using oral chemotherapeutic agents. *Am J Health Syst Pharm.* 2007;64(9 suppl 5):S8-S14.

74. Blasdel C, Bubalo J. Adherence to oral cancer therapies: Meeting the challenge of new patient care needs. *Clin Oncol*. 2006;(special report April):1-4.

75. Kirk MC. Insight into barriers against optimal adherence to oral hormonal therapy in women with breast cancer. *Clin Breast Cancer*. 2008;8(2):155-161.

76. Sharma S. Patient selection for oral chemotherapy. *Oncology (Williston Park).* 2001;15 (1 suppl 2):33-35.

77. Talpaz M, Silver RT, Druker BJ, et al. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. *Blood*. 2002;99(6):1928-1937.

78. DeMario MD, Ratain MJ. Oral chemotherapy: rationale and future directions. *J Clin Oncol*. 1998;16(7):2557-2567.

79. Mrozek-Orlowski ME, Frye DK, Sanborn HM. Capecitabine: nursing implications of a new oral chemotherapeutic agent. *Oncol Nurs Forum.* 1999;26(4):753-762.

80. Osborne CK. Tamoxifen in the treatment of breast cancer. *N Engl J Med*. 1998;339:1609-1618.

81. Smith IE, Dowsett M. Aromatase inhibitors in breast cancer. *N Engl J Med*. 2003;339:2431-2442.

82. Soran A, Nesbitt L, Mamounas EP,et al. Centralized medical monitoring in phase III clinical trials: the National Surgical Adjuvant Breast and Bowel Project (NSAPB) experience. *Clin Trials.* 2006;3(5):478-485.

83. Jacobson JO, Polovich M, McNiff KK, et al. American Society of Clinical Oncology/Oncology Nursing Society chemotherapy administration safety standards. *Oncol Nurs Forum*. 2009;36(6):1-8.

84. DiMatteo MR. Variations in patients' adherence to medical recommendations: A quantitative review of 50 years of research. *Med Care*. 2004;42(3):200-209.

85. Kennedy JT, I., Mackay K. Unfilled prescriptions of medicare beneficiaries: prevalence, reasons, and types of medicines prescribed. *J Manag Care Pharm.* 2008;14(6):553-560.

86. Banning M. Older people and adherence with medication: a review of the literature. *Int J Nurs Stud.* 2008;45(1):1550-1561.

87. Cleary KK, Howell DM. Prescription medication use and health-related quality of life in rural elderly. *Phys Occup Therap Geriatrics*. 2007;26(2):63-81.

88. Bagchi A, Esposito D, Kim M, Verdier J, Bencio D. Utilization of, and adherence to, drug therapy among medicaid beneficiaries with Congestive Heart Failure. *Clin Ther*. 2007;29(8):1771-1783.

89. Erlen JA, Sereika SM. Fidelity to a 12-week structured medication adherence intervention in patients with HIV. *Nurs Res*. 2006;55(suppl 2):S17-S22.

90. Waterhouse DM, Calzone KA, Mele C, Brenner DE. Adherence to oral tamoxifen: a comparison of patient self-report, pill counts, and microelectronic monitoring. *J Clin Oncol*. 1993;11(6):1189-1197.

91. Decker V, Spoelstra S, Miezo E, et al. A pilot study of an automated voice response system and nursing intervention to monitor adherence to oral chemotherapy agents. *Cancer Nurs*. 2009;32(6):E20-E29.

92. Mayer EL, Partridge AH, Harris LN, et al. Tolerability of and adherence to combination oral therapy with gefitinib and capecitabine in metastatic breast cancer. *Breast Cancer Res Treat.* 2009;117(3):615-623.

93. Hawwa AF, Millership JS, Collier PS, et al. The development of an objective methodology to measure medication adherence to oral thiopurines in paediatric patients with acute lymphoblastic leukaemia—an exploratory study. *Eur J Clin Pharmacol*. 2009;65(11):1105-1112.

94. Vinson M, Thomas-Welch K, Wen L, Stein B. Self-assessment of patients' knowledge and adherence to oral chemotherapy medications. *Oncol Nurs Forum*. 2009;36(3):60-61.

95. Simpson SH, Eurich DT, Majumdar SR, et al. A meta-analysis of the association between adherence to drug therapy and mortality. *BMJ*. 2006; 333(7557):15.

96. Obias-Manno D, Friedmann E, Brooks MM, et al. Adherence and arrhythmic mortality in the cardiac arrhythmia suppression trial (CAST). *Ann Epidemiol*. 1996;6(2):93-101.

97. Wei L, Wang J, Thompson P, Wong S, Struthers AD, MacDonald TM. Adherence to statin treatment and readmission of patients after myocardial infarction: a six year follow up study. *Heart.* 88(3):229-233.

98. Simpson RJ. Challenges for improving medication adherence. *JAMA*. 2006;296:2614-1616.

99. MacLeod A, Branch A, Cassidy J, McDonald A, Mohammed N, MacDonald L. A nurse/pharmacy led capecitabine clinic for colorectal cancer: results of a prospective audit and retrospective survey of patient experiences. *Eur J Oncol Nurs*. 2007;11(3):247-254.

100. MacDonald HP, Garg AX, Haynes RB. Interventions to enhance patient adherence to medication prescriptions: scientific review. *JAMA*. 2002;288(22):2868-2879.

101. Magai C, Consedine N, Neugut AI, Hershman DL. Common psychosocial factors underlying breast cancer screening and breast cancer treatment adherence: a conceptual review and synthesis. *J Womens Health (Larchmt).* 2007;16(1):11-23.

102. Miaskowski C, Dodd MJ, West C, et al. Lack of adherence with the analgesic regimen: a significant barrier to effective cancer pain management. *J Clin Oncol*. 2001;19(23):4275-4279.