Patient Adherence and Persistence With Oral Anticancer Treatment

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Abstract

Given the recent significant increase in the use of oral therapies in cancer management, an understanding of patients' adherence to and persistence with oral therapy is crucial. Nonadherence and early cessation may be substantial barriers to the delivery of valuable therapies, and may impair health. Potential obstacles to adherence and persistence include personal characteristics, treatment features, and system factors. Techniques for measuring adherence and persistence include self-report, pill counts, microelectronic monitoring systems (MEMS), prescription database analysis, and the assessment of serum or urine drug levels. This review article describes available data regarding adherence and persistence among patients with cancer, as well as studies of interventions to improve adherence. All reports of studies of adherence with oral cancer therapy that the authors could find on PubMed or in the reference sections of these PubMed-located articles were included. Adherence and persistence rates ranged from 16% to 100% with different therapies and different methods of measurement. Studies that included educational, behavioral, and multidimensional interventions to improve adherence were also described. **CA Cancer J Clin 2009;59:56-66. ©2009 American Cancer Society.**

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Introduction

Historically, patient-administered oral medications have played a relatively minor role in anticancer treatment compared with parenteral cytotoxic therapies. However, in the past decade, increasing attention has focused on the merits of oral therapy from the standpoints of drug delivery and patient preference, and the number of available agents has grown.[1,2] There are now more than 20 oral antineoplastic agents approved for use in the United States alone, and dozens more are currently in the pipeline.[3] Concurrent with the increasing use of oral agents, the potential problem of nonadherence in oncologic care and research has received greater recognition.[4-7] If patients do not take their medications, they will not be able to benefit from them. For example, patients who were found to fill fewer than 70% of their tamoxifen prescriptions had an increased risk of death according to a recently published abstract.[8] In the current article, we reviewed issues of adherence and persistence in medical care, and updated the available evidence regarding adherence with oral anticancer treatment.

The International Society for Pharmacoeconomics and Outcome Research (ISPOR) recently defined adherence as synonymous with compliance, that is, "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."[9] Adherence is a term that is often preferred to compliance because it is generally believed to have a less pejorative and less judgmental

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connotation. The ISPOR group distinguished adherence from persistence, which was defined as the duration of time from the initiation to the discontinuation of therapy.[9] Most of the data in oncologic populations do not address adherence and persistence separately, but whenever possible we attempt to discern between the two. Most commonly, the terms adherence and persistence are used regarding oral medication use, but they also may apply to the use of medically prescribed devices, exercises, or counseling sessions. Optimal adherence and persistence occur when a patient follows his or her prescribed treatment regimen exactly. A patient is optimally adherent if no doses are missed, no extra doses are taken, and no doses are taken in the wrong quantity or at the wrong time. A patient has optimal persistence if he or she takes a medication as long as it is prescribed. Overadherence may also be problematic because safety is impaired if patients are taking too much of a medication.[10] Overpersistence is likely rare for prescription drugs unless excess prescriptions have been provided. To our knowledge, there currently is no consensus regarding a definition for "adequate adherence," with investigators using ranges of between 80% and 95%, although there are limited data to support this threshold.[11] The following classification scheme has been proposed to account for a range of adherent behaviors: adherer, partial adherer, overuser, erratic user, partial dropout, and dropout.[12]

Measurement of Adherence and Persistence

Several different methods exist to measure adherence and persistence, but no method is without substantial limitations. Patient awareness that adherence is being measured may impact the degree of adherence because patients who are cognizant of ongoing observation may demonstrate improved behavior. This influence of the observation on the outcome of interest is termed the "Hawthorne effect."[5] Self-report, in which patients are asked to recall how accurately they followed their prescribed regimen, has been repeatedly shown to suffer response bias, with patients usually over-reporting rates of adherence because of a desire to please providers.[13] Patient-completed medication diaries may provide flawed information regarding adherence for the same reason, although they may be less susceptible to recall bias because the patient is asked to record each dose as it is taken.

Pill counts, requiring patients to return unused pills at each visit so that the number of missed doses can be calculated, have also been shown to overestimate the number of pills actually taken.[14,15] Patients may throw away missed doses to avoid being viewed as nonadherent. Nonetheless, pill counts are often used as an alternative or an adjunct to self-report. However, pill counts provide no information concerning the timing of doses, which may be a critical factor in treatment effectiveness in some settings.

Serum or urine drug or metabolite levels are more objective measures of adherence and persistence, but do not describe the timing of doses and can still be manipulated by patients (medication dosing can be resumed or extra doses of medication can be taken before an office visit to avoid appearing nonadherent). Also, because of pharmacokinetic variability in drug absorption, distribution, metabolism, and excretion, ranges that are consistent with adherence may be wide. Furthermore, accurate measurement of serum or urine drug metabolites is only available for certain drugs (eg, prednisone and 6-mercaptopurine [6-mp]). However, in some diseases, intermediate markers of drug use can also be useful. For example, plasma viral load in patients with the human immunodeficiency virus (HIV) can act as a surrogate for adherence to antiviral therapy. However, most of the oral drugs used to treat cancer do not produce similar intermediate markers of adherence that can be easily measured in a clinical setting.

A novel method for the measurement of adherence is the microelectronic monitoring system (MEMS). The MEMS system consists of an "intelligent" cap on a pill bottle that electronically records every time the cap of the pill bottle is removed. MEMS data thus provide a computerized record of each date and time the bottle is opened. Although MEMS monitoring is considered to be less subject to patient manipulation, a pill may not be ingested every time the pill bottle is opened. Even with these more objective measures, data may still be influenced by the Hawthorne effect and patient desire to appear optimally adherent. Furthermore, the MEMS technique is quite expensive and therefore is used primarily in clinical research and is not feasible in many settings.

When information technology allows for the analysis of prescription refills, adherence can be calcu-

lated as the proportion of days within a given time period during which a patient has filled prescriptions (ie, "days covered"). Average days covered can then be calculated for a large population over a period of time, or adherence can be defined as the percentage of patients who have an adequate amount of filled prescriptions available for the time under study. Using this approach, it is possible that some patients may miss and/or double up on pills and still refill prescriptions on time, and there is no information provided regarding the timing of doses. Furthermore, some prescription refill studies fail to separate nonadherence from lack of persistence because they simply estimate the proportion of days a patient had pills available, not distinguishing between those who are taking the medication incorrectly and those who stop the medication entirely.[16] Nevertheless, the strength of studying refill rates is that it provides the most objective measure of adherence in a large population over a long period of time. This methodology, often using pharmacy or insurance records, avoids the Hawthorne effect as well as patient manipulation for social desirability because subjects would generally not be aware that their refill rates would eventually be reviewed.

Consequences of Nonadherence and Nonpersistence

Suboptimal adherence to oral therapies can have multiple consequences. Poor adherence and persistence can severely impede the efficacy of oral regimens.[17] If a physician is not aware that a patient is not taking an oral therapy as prescribed, he or she may attribute progression of the disease to a lack of activity of the drug, and therefore may unnecessarily change a regimen.[18] Nonadherence and nonpersistence in a variety of patient populations has been associated with an increased consumption of healthcare resources, including more physician visits, higher hospitalization rates, and longer stays.[19-22] The toxicities of a drug may be increased, especially if a patient is taking doses too close together or at the wrong time of day.

When patients participating in clinical trials are nonadherent, inaccurate conclusions and flawed dosing recommendations may result.[23-25] Therefore, some studies have included assessments of adherence to try to limit this type of error.[26,27] However, adherence in a clinical trial tends to be much higher than what has been observed outside of the trial setting because self-report, with its associated biases, is the most commonly used assessment of adherence in clinical trials. Furthermore, rates of adherence with oral medication in clinical studies are usually 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.[5,11]

In many nononcologic diseases, research suggests that most patients achieve a moderate yet not optimal level of adherence. In a large study by Avorn et al of patients aged older than 65 years with prescription drug coverage as part of Medicaid/Medicare or Quebec's provincial medical care program, lipid-lowering prescriptions were unfilled for approximately 40% of 1 year (1990-1991).[18] After 5 years (in 1995-1996), only 52% of the surviving patients in the United States were still filling any lipid-lowering prescriptions at all. The clinical ramifications of nonadherence may be medically significant. In a smaller prospective study of 99 patients with ulcerative colitis, Tindall et al found that the most significant factor leading to recurrence of disease was nonadherence to therapy, with a hazards ratio of 5.5 (95% confidence interval [95% CI], 2.3-13.0) for those who took more than versus those who took less than 80% of their prescribed medication.[28]

To our knowledge, there are little data in oncology published to date regarding the effects of nonadherence and nonpersistence. The importance of nonadherence likely varies from drug to drug. For example, the therapeutic benefit derived from agents with longer half-lives may be minimally compromised by missed doses. For example, because tamoxifen and its metabolites have 7-day to 14-day half-lives whereas the half-lives of letrozole and anastrozole are approximately 2 days and that of exemestane is only 27 hours, the consequences of 1 missed dose may be greater in a patient receiving 1 of the aromatase inhibitors rather than tamoxifen.[29,30] However, this concept requires further study. Given the challenging economics of healthcare, it is problematic that patients and third-party payers are paying for medications that may not be used correctly. More than half of the total medications prescribed annually in the United States may be used incorrectly, leading to

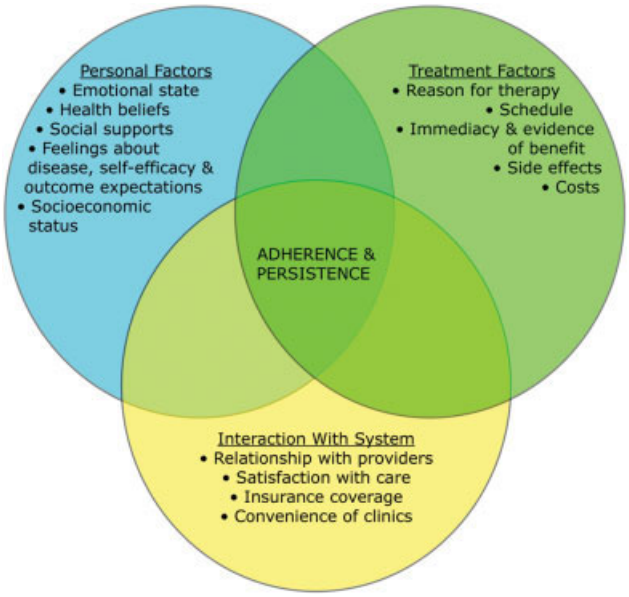

FIGURE 1. Model of Adherence and Persistence.

inferior outcomes and an estimated cost to society of $100 billion.[31]

Barriers to Adherence

Numerous studies have tried to elucidate why patients do not take medications as directed. In a population with multiple sclerosis, the factors that were found to be associated with missing doses of immunomodulatory agents were different from those associated with stopping the drugs entirely.[32] It is unclear whether this is also true with medications for cancer. Studies are often limited by the information available regarding potential reasons for nonadherence, and findings regarding standard demographic factors have been inconsistent to date.[33] For example, age has not been shown to be a consistent predictor of adherence except that adolescents are significantly less adherent than other pediatric patients.[34-36] Reasons for nonadherence are complex in most situations.[37] Factors that have been frequently associated with nonadherence to recommended medical therapies include individual patient characteristics, features of the disease and the treatment regimen, and aspects of the medical care system. A graphical biopsychosocial model of adherence (Fig. 1) depicts the complexity of adherence. Some aspects of treating regimens may be particularly associated with nonadherence. A large meta-analysis of 76 studies demonstrated that adherence is adversely proportional to medication dosing frequency.[38] In primary care settings, the overuse of drugs has been documented in cases in which patients are either confused about what they should be taking or believe that taking more medication than prescribed will add to the therapeutic benefit they experience.[39,40]

Conventional behavioral models have been applied to medication adherence, including the Health Belief Model, which focuses on: 1) the individual's evaluation of his or her own health condition, including disease severity and his or her own perceived vulnerability or sensitivity to the disease state; 2) the individual's evaluation of the risks and benefits of adherence to medication; and 3) a stimulus or "cue to action" that is either internal or external to prompt the individual to take the medication.[41]

Pediatric Populations

To the best of our knowledge, adherence has not been well-studied in young adults; the limited evaluation of adherence in children suggests rates of adherence ranging from 41% to 98% (Table 1).[35,36,42-46] Although Lansky et al found that girls and boys aged younger than 15 years were equally adherent when prescribed oral prednisone for acute lymphoblastic leukemia (ALL), characteristics that were correlated with adherence differed by age and sex. For example, anxiety was found to be positively associated with adherent behaviors in girls, whereas parental hostility and parental anxiety were positively associated with adherent behaviors in boys.[42] Two large studies in childhood ALL, one by Lancaster et al[36] and the other by Lennard et al,[43] both demonstrated concerning lapses in the self-administration of oral 6-mp based on serum levels of metabolites, especially in adolescents. Tamaroff et al reported that adolescent adherence is correlated with how well a patient understands the disease, including causality and prognosis; how much perceived vulnerability and future orientation he or she has; and lower levels of denial.[44]

Adult Populations

Although there is evidence that adult patients with nononcologic chronic disease on average take only half of their prescribed medications, adherence and persistence have been traditionally assumed to be better in cancer patients due to the perceived understanding of the risks of not taking medications as prescribed.[11,47,48]

This may vary by cancer, as well as by other patient-specific and drug-specific variables. For example, Veronesi et al reported that the permanent discontinuation of tamoxifen occurred in 26.7% of women receiving primary prevention for breast cancer; however, the average discontinuation rate in a variety of trials of adjuvant tamoxifen for patients with established breast cancer was only 15.1%.[49] In general, rates of adherence to and persistence with oral cancer therapies have been documented to range between 16% and 100% in adult populations (Table 2).[8,21,27,48,50-62]

Until recently, the vast majority of available data regarding adherence to and persistence with cancer therapies in adult populations have been based on small studies of self-reporting by patients, which may be quite biased as noted previously.[63] Much of this work has examined the use of oral therapy for the treatment of breast cancer. In a report by Grunfeld et al, of 110 patients with early stage breast cancer who were questioned regarding tamoxifen use, 12% reported nonadherence.[58] In a study by Demissie et al, 15% of postmenopausal women receiving tamoxifen for early stage breast cancer (26 patients of a total of 303) admitted in telephone interviews to stopping the drug by 3 years from the time of diagnosis.[64] This study found better odds of tamoxifen use in patients who were ages 65 to 74 years (compared with those ages 55 to 64 years), had stage II disease (compared with those with stage I disease), were estrogen receptor positive, saw a greater number of breast cancer physicians, and had better perceptions of their abilities to discuss treatment options with physicians. Those who had better physical function, had received standard primary tumor therapy, and had obtained helpful breast cancer information from books or magazines had lesser odds of tamoxifen use. The reasons for this pattern of nonpersistence are unclear. Similar rates of discontinuation were found in a 516-patient telephone interview study by Fink et al and Lash et al, with 17% of patients stopping tamoxifen by 2 years,[65] and 31% stopping it by 5 years from the time of diagnosis, respectively.[66] Nonpersistence was found to correlate with the patient's belief about the risk-benefit ratio. Another self-report study performed in India by Murthy et al[56] found that 24% of 53 breast cancer patients missed at least 1 dose of tamoxifen per week, with a patient survey indicating that forgetting doses was the most common reason for missed pills. Age, socioeconomic parameters, and duration of use were not found to be correlated with adherence, but the sample size was small.[56] In an older study, Lebovits et al[21] reported a similarly high rate of nonadherence among 51 breast cancer patients who had been prescribed oral cyclophosphamide and/or prednisone. Interviews at 5 timepoints over a 6-month period revealed a 43% rate of nonadherence, with more adherence found in the academic setting compared with community-based treatment settings as well as in patients with higher incomes.[21] In a study conducted in the United Kingdom among 131 women who were receiving hormonal therapy, Atkins et al found that 54% of those

TABLE 1. Studies of Pediatric Adherence to Oral Antineoplastic Agents

CANCER	NO.	ORAL THERAPY	ADHERENCE MEASURE	ADHERENCE RATE	TIME PERIOD	STUDY
Leukemia or non-Hodgkin lymphoma	52	Prednisone	Urinary metabolites	Overall: 67% Adolescent: 41%	Not stated	Smith 1979[45]
Acute lymphocytic leukemia (ALL)	31	Prednisone	Urinary metabolites	58%	Not stated	Lansky 1983[42]
ALL	327	6-mercaptopurine (6-mp) maintenance	Two metabolites in red blood cells	97% with some present; 90% not, with both in lowest quartile	≥7 days	Lennard 1995[43]
ALL	496	6-mp	Two metabolites in red blood cells	98% with some present	Not stated	Lancaster 1997[36]
Variety	46	Variety: tamoxifen, prednisone, 6-mp, methotrexate, and procarbazine	Self-report that missed ≤1 dose/mo; serum prednisone	50 wk: 65% adherent, 25% with occasional, and 10% with frequent missed doses	50 wk	Tebbi 1986[35]
ALL and Hodgkin lymphoma	50	Prednisone or prophylactic penicillin	Serum dehydroepiandrosterone sulfate suppression (for prednisone) and urinary growth inhibition assay (for penicillin)	Prednisone: 48% Penicillin: 52%	Not stated	Tamaroff 1992[44]; Festa 1992

NOTE: Adapted from Partridge 2002.[5]

TABLE 2. Studies of Adult Adherence to Oral Antineoplastic Agents Over Time

YEAR	CANCER	NO.	ORAL THERAPY	ADHERENCE OR PERSISTENCE MEASURE	ADHERENCE OR PERSISTENCE RATE	TIME PERIOD	STUDY
1987	Hematologic malignancy	108	Prednisone and allopurinol	Serum metabolites	Prednisone: 26.8% Allopurinol: 16.8%	6 mo	Levine 1987[50]; Richardson 1988
1990	Breast cancer	51	Cyclophosphamide and/or prednisone	Self-report that 90-110% taken	53% overall with both drugs	6 mo	Lebovits 1990[21]
1992	Lymphoma	21	Chlorambucil, prednisolone, or dexamethasone	Microelectronic monitoring system (MEMS)	100% (standard deviation [SD]: 20.6%)	852 d	Lee 1992[52]
1993	Breast cancer	26	Tamoxifen	Self-report Pill count MEMS	97.9% (SD: 3%) by self-report; 92.1% (SD: 9.8%) by pill counts; 85.4% (SD: 17.2%) by MEMS	Mean of 2.92 mo	Waterhouse 1993[48]
1993	Small cell lung cancer	12	Etoposide	MEMS	93.2% (SD: 12%)	298 d	Lee 1993[53]
1996	Ovarian cancer	11	Altretamine	MEMS	97.4% (SD: 6.9%)	294 d	Lee 1996[54]
2000	Colon cancer	57	Uracil-tegafur	Self-report Physician interview Urine level	94.4% at 3 mo, 94.7% at 1 y by self-report and interview; 94.7% in range by urine testing of 38 patients at various timepoints	1 y	Sadahiro 2000[55]
2002	Breast cancer	53	Tamoxifen	Self-report	76% missed <1 dose per wk	6 mo	Murthy 2002[56]
2003	Breast cancer	2,378	Tamoxifen	Prescription refill records	77% filled prescriptions that covered at least 80% of doses over the 1st y; 50% did so by 4th y	4 y	Partridge 2003[57]
2005	Breast cancer	110	Tamoxifen	Self-report	88% adherent	Not stated	Grunfeld 2005[58]
2006	Myelodysplastic syndrome	90	Topotecan	MEMS	90%	5-10 d	Klein 2006[59]
2006	Breast cancer	131	Tamoxifen	Self-report	55% reported nonadherence to medication frequently or occasionally	Single point in time	Atkins 2006[60]
2007	Breast cancer	2,816	Tamoxifen	Prescription refill records	77.9% at 1 y; 64.8% at 3.5 y	3.5 y	Barron 2007[61]
2007	Breast cancer	1,633	Tamoxifen	Clinical notes, audit records, cancer registry data, prescription records	93% median (95% confidence interval, 84-100%)	2.4 y	Thompson 2007[8]
2008	Breast cancer	12,391	Anastrozole	Prescription refill records	78-86% of d were covered by filled prescriptions in Year 1; 62-79% of d were covered by filled prescriptions in Year 3	3 y	Partridge 2008[62]
2008	Breast cancer	161	Capecitabine	MEMS	76% took at least 80% of doses	6 cycles (14/21 d)	Partridge 2008[27]

NOTE: Adapted and updated from Partridge 2002.[5]

prescribed tamoxifen and 61% of those prescribed an aromatase inhibitor reported instances of nonadherence.[60] Younger age and disliking aspects of the medication were associated with nonadherence. Patients who reported feeling less control over their healthcare were more likely to report that the reason for nonadherence was personal choice (rather than forgetfulness).[60]

Persistence has also been examined in the context of large, prospective, clinical treatment studies. MA-17, a large clinical trial of adjuvant hormonal therapy performed in 5,157 postmenopausal women, found that 95.5% of those randomized to letrozole had not discontinued it after 29 months.[67] Somewhat higher rates of discontinuation were found at 36 months for exemestane (15.5%) and tamoxifen (12.7%) in the 4,742 women in the Intergroup Exemestane Trial (IES).[68] Of the 6,241 women included in the Arimidex and Tamoxifen Alone or in Combination (ATAC) trial, only 76% of the anastrozole-treated women and 72% of the tamoxifen-treated women were still taking their medication by 47 months after

diagnosis.[69] A meta-analysis of studies that evaluated persistence with tamoxifen or an aromatase inhibitor reported that overall, 23% to 28% of patients followed in clinical trials for at least 4 years discontinued their oral hormonal therapy earlier than recommended.[70] The authors, Chlebowski and Geller, described that the analysis of 2 studies of patients not taking part in clinical trials found an even higher (30%-50%) rate of discontinuation.[70] These low rates of persistence are sobering given the importance of endocrine therapy in the management of hormone receptor-positive breast cancer.

Several studies have evaluated adherence to oral chemotherapies in patients with other cancers. Sadahiro et al[55] found an exceptionally high rate (94%) of agreement between patient self-report of adherence, physician interview of patients regarding adherence, and urine levels of drug metabolites in a study of weekday-on/weekend-off oral uracil-tegafur as adjuvant chemotherapy for colon cancer. All revealed greater than 90% adherence, but by these authors' definition, these "adherent" patients could still have reported missing up to 3 of the 15 doses each week.[55] In a study of 108 patients with hematologic malignancies by Levine et al,[50] examination of serum drug metabolites demonstrated that only 26.8% of patients had adequate levels of prednisone and 16.8% had adequate levels of allopurinol. However, the patients' self-reports in this study overestimated adherence by a factor of 2.[50]

Analysis of adherence by MEMS frequently detects higher rates of adherence, perhaps due to the Hawthorne effect, although this has not been true in all studies. Adherence rates of 90% were observed by Klein et al in a study that used MEMS to document adherence to topotecan in 90 patients with myelodysplastic syndrome.[59] Similarly, a MEMS analysis by Lee et al demonstrated a 100% adherence rate among 21 adult lymphoma patients taking chlorambucil, prednisolone, or dexamethasone for lymphoma.[52] Other very small studies have confirmed that MEMS documents high adherence (Lee et al found a 93.2% adherence to etoposide in 12 patients with small cell lung cancer, whereas Leventhal et al found a 97.4% adherence to altretamine in 11 patients with ovarian cancer).[53,71] However, among a population of 161 breast cancer patients in a Cancer and Leukemia Group B (CALGB) study who were receiving capecitabine and were being monitored by MEMS, Partridge et al reported that only 76% took at least 80% of their doses[27]; 11% took less than 60% of the doses as instructed, and 14% took 60% to 79% correctly. Furthermore, MEMS device data taken from a study by Waterhouse et al regarding 3 months of tamoxifen use revealed significantly lower adherence rates than did self-report or pill counting.[48] Interestingly, the authors reported that although patients were asked to only open the pill container if they were going to take the medication, they were not directly informed that their adherence was being monitored.[48]

Researchers have increasingly used the evaluation of insurance or commercial pharmacy databases containing records of medication refills to evaluate adherence and persistence in oncology. Because of the chronic nature of hormonal therapy for breast cancer, this has been an ideal method for studying rates of adherence in large populations. In what to our knowledge is the first of these studies, Partridge et al found that the mean percentage of days during the first year of tamoxifen therapy during which a filled prescription was available was 87% among 2,378 patients with early stage breast cancer.[57] Approximately 77% of women had filled prescriptions for tamoxifen adequate to cover greater than 80% of the year. In a subset of 492 patients for whom long-term data were available, filled prescriptions were available for only 50% of days during the fourth year of treatment. Adherence rates were lower in the young (age younger than 45 years), the very old (aged older than 85 years), and nonwhite women.[57] However, because this study did not distinguish adherence from persistence, some of those women who were classified as nonadherent may actually have been nonpersistent, and therefore rates of nonadherence in those who did not stop the drug entirely may have been overestimated. Persistence was the primary endpoint in a study by Barron et al,[61] which evaluated a national prescribing database of 2,816 Irish women older than 35 years who were starting tamoxifen therapy between January 2001 and January 2004. These authors found that 22.1% of women had discontinued therapy (not taken tamoxifen for more than 180 days) by 1 year and 35.2% had done so by 3.5 years.[61] Defining discontinuation of therapy as only greater than 60 days without tamoxifen, Owusu et al found a 49% rate of discontinuation in an analysis of the pharmacy records of 961 patients with early stage breast cancer who were prescribed tamoxifen at age 65 years or

older.[72] However, some of these women may have restarted tamoxifen later. In an effort to determine whether adherence was different with newer oral hormonal therapies with different costs and side effect profiles, Partridge et al[62] evaluated adherence with initial aromatase inhibitor therapy in a study of longitudinal claims data from 3 large commercial health programs. Mean adherence to anastrozole was found to range from 82% to 88% over the first 12 months of therapy in women with early stage breast cancer. Approximately 19% to 28% of women had fewer than 80% of days covered by anastrozole prescriptions. Mean adherence decreased to 62% to 79% in the third year of therapy. Patients who never filled a single prescription were not captured by pharmacy records and those who developed early metastatic disease because of nonadherence were not included; in addition, persistence was not evaluated separately.[62] Overall, these findings likely reflect a substantial drop in both adherence and persistence over time. Another investigation, which to our knowledge has only been published as an abstract to date, uniquely performed a combined review of the clinical notes, audit notes, cancer registry data, and prescription records of all women treated for breast cancer at a regional cancer center between 1993 and 2002. This study revealed that the duration of tamoxifen use and greater adherence during that time of use were both associated with improved survival.[8]

Interventions to Improve Adherence and Persistence

There is some evidence that interventions to encourage the accurate self-administration of oral therapies can be effective.[73] Interventions may be educational, behavioral, affective, or multidimensional.[74] One small behavioral intervention study by Macintosh et al of 25 patients comparing the use of daily pill boxes versus conventional pill bottles of capecitabine found that patients preferred daily boxes, but adherence did not significantly differ between the two mechanisms.[75] However, patient education by physicians, nurses, pharmacists, and other providers may be very helpful (Table 3). For example, education, home psychologic support and restructuring, or training in pill taking (including practicing self-medication in a controlled environment) all were found to improve the proportion of patients with acceptable drug levels from below 20% to above 40% in the study by Levine et al of serum metabolites of prednisone and allopurinol.[50] Furthermore, a Cochrane review by Beney et al of educational pharmacist counseling regarding oral drugs for nononcologic diseases revealed improved patient outcomes in 10 of 13 studies and improved adherence in 3 of 6 studies.[76] Likewise, Lee et al performed a multiphase, prospective, randomized controlled trial at the Walter Reed Army Medical Center that demonstrated that intensive multidimensional pharmacy care (individualized medication education, blister pack dispensing, and follow-up with a pharmacist every 2 months) improved medication adherence in elderly men taking at least 4 chronic medications.[77] Given the Hawthorne effect, systematic monitoring of patient pill taking may be an effective way to improve both adherence and persistence. A survey of 42 compre-

TABLE 3. Predicting and Improving Adherence and Persistence

SIGNS AND PREDICTORS OF POOR ADHERENCE AND PERSISTENCE
Missed appointments, inadequate follow-up Poor patient-provider relationship Unfilled prescriptions Adverse effects from medication, medication cost Lack of belief in treatment Psychologic problems, particularly depression
INTERVENTIONS FOR IMPROVING ADHERENCE
Increased accessibility to healthcare • More convenient follow-up appointments • Access to pharmacists, behavioral specialists, social workers Improved dosing plan • Simplify schedule • Supply pill boxes to organize doses • Reminders to take medications (wristwatch with alarm, support from family and/or friends) Educational intervention to increase patient's understanding of: • Disease characteristics • Risks and benefits of treatment • Proper use of medication Physician initiatives • Simplify the oral regimen • Increase the patient's understanding of disease and participation in decision-making • Listen to the patient • Learn about drug costs and insurance coverage • Reinforce adherent behaviors

NOTE: Adapted from Osterberg & Blaschke 2005.[11]

hensive cancer centers by Weingart et al found that 10 reported asking patients to bring in pill diaries and 9 reported using pill counting to routinely monitor adherence.[10]

Future Studies

Additional research is needed to investigate adherence to and persistence with the many new oral targeted cancer regimens, including imatinib, erlotinib, sunitinib, and lapatinib. It will be important to investigate in which diseases and with which therapies outcomes are significantly impaired by missed doses, such that interventions to optimize adherence can be targeted to the patients who are most in need. For example, with tyrosine kinase inhibitors, it is unclear whether side effects such as rash and diarrhea act to increase adherence (because patients can see an effect) or decrease adherence (to avoid the unpleasant symptoms). Surveying patients to determine their opinions and recall of adherence to the prescribed regimen is helpful,[78] but it is likely other techniques that more accurately reflect actual practices will also be required. It is possible that combining measures of adherence and persistence may yield the most accurate results.[11] Furthermore, studies are needed to clarify whether different groups of patients face unique barriers to adherence and persistence and whether there are efficacious interventions to reduce these based on a biopsychosocial model of adherence. For example, it will be important to assess whether changing the insurance coverage and co-pay for a prescription alters adherence to the medication. Analysis of the costs and benefits of these interventions will also be valuable. The amount of therapeutic improvement that can be obtained by implementing various adherence interventions is not known.

Suggestions for Optimizing Adherence

Providers should consider asking patients whether they are taking their medications as prescribed and whether the regimen is causing them distress or side effects. It is important that physicians monitor the adherence rates in their practices overall and with individual patients. For clinicians treating patients outside of clinical trials, the simplest method of measurement of adherence and persistence may be self-report (asking patients whether they are still taking a medication and how many pills they have missed since their last office visit). Discussing the importance of adherence may be beneficial because it may spur those with poor adherence to improve and may encourage those with good adherence to continue. For patients who report poor adherence, clinicians may want to recommend or provide daily pill boxes or medication diaries for assistance. When feasible, on-site pharmacies and consultations with a pharmacist should be encouraged because this may facilitate adherence.[10]

Conclusions

Patient adherence to therapeutic regimens will be increasingly relevant in medical oncology as additional oral treatments are adopted for use in cancer care. Data are scarce regarding how well cancer patients adhere to and persist with their medication regimens, particularly those with malignancies other than breast cancer. Measuring and studying adherence to oral chemotherapies is difficult because a patient who is aware of being observed may demonstrate more adherence than the average patient receiving the same therapy. Although the impact of nonadherence and nonpersistence may differ between clinical care and research, they are important in both arenas. Because suboptimal adherence and discontinuation of therapy both may adversely impact the efficacy and toxicity of a medication, it is important that they be measured and maximized. Therefore, systematic assessment of adherence and persistence should be included in phase 3 trials of oral chemotherapies as well as in off-study treatment with oral antineoplastic agents. Further research will also be needed to explore the predictors of nonadherence and nonpersistence and to develop better methods for measurement and intervention. ■

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