Assessment and Measurement of Medication Adherence: Oral Agents for Cancer

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Despite efforts by clinicians and pharmaceutical manufacturers to encourage adherence to oral agents for cancer (OACs), adherence rates are sub-optimal (Bassan et al., 2014; Streeter, Schwartzberg, Husain, & Johnsrud, 2011). Evidence suggests that adherence to OACs is a significant clinical problem that may affect treatment success (Bozic et al., 2013; Gebbia, Bellavia, Ferraiù, & Valerio, 2012; Mitchell, Porter, & Manias, 2014; Puts et al., 2013). This article will report on methods to assess and measure medication adherence by patients with cancer to inform clinical practice.

Defining Medication Adherence

*Adherence* needs to be defined prior to assessment and measurement. For the current review, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) definition was used: 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 for the duration of time from initiation to discontinuation of therapy (Cramer et al., 2008).

This allows *underadherence*—taking less medication than prescribed (e.g., missing a daily dose, not starting a cycled drug on the day prescribed)—and *overadherence*—taking more medication than prescribed (e.g., doubling up on doses on the day after a missed dose, taking more pills than prescribed, taking the medication when off cycle) or taking doses too close together—to be examined. ISPOR’s definition of adherence provides a means to assess and measure all dimensions of treatment with OACs.

Background: Clinicians are challenged to find ways to assess and measure adherence to oral agents for cancer (OACs).

Objectives: The purpose of this article is to report on available ways to assess and measure medication adherence by patients with cancer.

Methods: Tools examined include the Morisky Medication Adherence Scale (MMAS) and the Adherence Estimator, which are able to predict risk of nonadherence. Adherence Starts With Knowledge (ASK®)-12 and the Brief Adherence Rating Scale (BARS) are likely to be effective for predicting nonadherence and measuring adherence rates.

Findings: Additional research needs to focus on the testing of reliable and valid tools that are sensitive and specific to patients with cancer who are prescribed OACs. The authors found that the MMAS and Adherence Estimator tools may be useful at predicting risk of medication nonadherence, and the ASK-12 and BARS may be useful for measuring rates of adherence. Tools could be modified to a specific clinical setting and used in a standardized format so that nurses can assess risk of medication nonadherence and measure adherence rates of OACs.
drug. Less than an adequate therapeutic dose can occur because of toxicities from side effects of treatment, causing dose reductions or stoppages, or because of problems with obtaining the medication, resulting in dose delays (Bozic et al., 2013; Gebbia et al., 2012; Puts et al., 2013). An additional problem is the relationship between therapeutic dose and tumor response or survival. What is not known is whether 80% of the dosage is adequate, or if 90% may be effective (Alberto, 1994). Therapeutic dosing often is measured using relative dose intensity (RDI), the ratio of dose taken over a period of time in relation to what was prescribed (Amgen, Inc., 2008; Loibl et al., 2011; Raza, Welch, & Younus, 2009). Maintaining RDI reduces the survival of resistant clones, increases the percentage of cells killed per dose, and decreases intervals between treatment cycles, resulting in greater treatment efficacy. As a consequence, to ensure RDI, most oncologists prefer 100% OAC adherence.

The Complexities of Oral Anticancer Agents

OAC regimens may be simple or complex. Simple OAC regimens are once-daily dosing. Complex regimens are more than once-a-day dosing, on- and off-cycling, two or more drugs, or when supportive care drugs are prescribed (e.g., dexamethasone) (Spoelstra et al., 2013). Many OAC regimens are complex and may influence the ability to assess and measure adherence.

Obtaining OACs also may affect assessment and measurement of adherence. OACs can be expensive, ranging from $10,000–$100,000 per year for a course of treatment; consequently, insurers often require small quantities of OACs to be dispensed to reduce wastage (Express Scripts, 2011). Oncologists also may be unsure about OAC drug tolerance when changing regimens or for those who are in later lines of treatment, so they prescribe small quantities. In addition, OACs frequently are dispensed by specialty pharmacies, which may lead to problems with shipping, again delaying dosing (Schneider, Hess, & Gosselin, 2011).

Underadherence can occur if patients do not have the medication, if they forget, or if they become confused about how much or when to take their medication. Overadherence can occur if patients are uncertain or confused about cycling, if they start a prescription on receipt of a shipment prior to the date the OAC is to be taken, or if they are unsure about the number of pills to be taken for each dosage. According to the Institute for Safe Medication Practices (2014), a patient with brain cancer overdosed after a pharmacy dispensed different dosages of the same drug for the same prescription; the drugs were to be taken sequentially and instead were taken concurrently. The patient died from overdose of the oral agent, and a safety alert was sent out.

Methods to Assess and Measure Adherence

Despite the importance of medication adherence, limited research has been conducted on assessment and measurement. Assessment is the act of collecting information to make a judgment (e.g., self-reporting medication adherence), and measurement is the process of measuring or the assignment of numbers to an event (e.g., 80% rate of medication adherence) (Jimmy & Jose, 2011). Methods to assess and measure medication adherence are discussed in this article, along with their limitations.

Direct Methods

Direct measures of medication adherence include drug assays of serum or urine, use of drug markers with a target medication, and direct observation of the patient ingesting the medication (Farmer, 1999). Serum or urine assays only are available for certain drugs (e.g., 6-mercaptopurine); none are available for OACs, nor do OAC drug markers exist. Direct observation of patients taking OACs is costly and impractical because administration occurs in the home setting. Therefore, direct measures of adherence to OACs are not available, are impractical, or are too expensive to use in the clinical setting.

Indirect Methods

Indirect measures of medication adherence imply that the medication has been taken by the patient. Examples include various self-reports (e.g., questionnaires, diaries, calendars), as well as pill counts, electronic medication monitors, and review of prescription records and claims (Farmer, 1999). Technology-based (e.g., mHealth) devices that indirectly measure adherence are becoming available, but effectiveness has not been established.

Self-report: Patient self-report has been used extensively to assess medication adherence, particularly in clinical practice. However, self-report tends to overestimate adherence because questions asked may not be specific enough to evaluate all dimensions of adherence (i.e., dosage, time taken, and persistence) (Ayoade & Oladipo, 2012; Escalada & Griffiths, 2006; Font et al., 2012). In addition, self-report repeatedly has shown to suffer response bias, with over-reported rates of adherence because of patient desire to please providers (Jasti, Siega-Rizt, Cogswell, & Hartzema, 2006). Cognitive decline during aging and disease or because of medication effects also may influence recall and whether the medication was taken properly (Insel, Morrow, Brewer, & Figueredo, 2006). Some clinicians use patient-completed diaries; however, inaccurate adherence rates may occur because of poor recall or bias. Nevertheless, a diary may be less susceptible to bias when patients are asked to record each dose when taken (Ruddy, Mayer, & Partridge, 2009).

Pill counts: A pill count is a manual tally of the number of pills remaining (i.e., comparing the number of doses remaining in a container with the number that should remain). Studies have found that pill counts overestimate adherence, often because of a patient throwing away pills (Vrijens & Urquhart, 2014). Pill counts often are used in research to measure medication adherence but are time-consuming and often not practical in the clinical setting.

Electronic monitoring systems: Electronic medication monitoring systems to measure medication adherence (e.g., MEMS®) often are used during clinical trials (Badiee et al., 2012; Park, Howie-Esquível, Chung, & Dracup, 2014; Schmitz, Sayre, Stotts, Rothfieldisch, & Mooney, 2005). Electronic medication monitoring systems consist of an “intelligent” cap that electronically records the date and time the top of the pill bottle or pill tray is opened. Although this provides an objective measure of pill bottle opening, whether ingestion of the medication occurred is not known. Use of electronic medication monitoring systems also may be influenced by the Hawthorne effect, in which the patient desires to please the provider. Electronic medication...
monitoring systems on the market are expensive and not yet feasible for use in the clinical setting.

**Pharmacy records and claims:** Medication adherence often is examined using proportion of days covered (PDC), a prescription interval-based measure using pharmacy dispensing or claim records (Karve et al., 2009a, 2009b; Nau, n.d.). PDC is calculated by summing the number of days in a time period “covered” by the medication divided by the number of days in the period. PDC can provide a conservative estimate of medication adherence when drugs are switched or if two OACs are prescribed. PDC also can be adjusted when patients have overlapping prescriptions dispensed for an identical (e.g., generically equivalent) medication, based on the premise that when a prescription is refilled before the preceding medication supply is exhausted, the patient finishes the supply of the preceding prescription before starting the new supply. Although an effective means of measuring medication adherence in research, PDC is not practical for use in the clinical setting; most clinicians do not have access to pharmacy dispensing or claims records, and calculation is time-consuming.

**Tools to Assess and Measure Medication Adherence**

Seven tools were found in the literature to assess the risk of nonadherence or to measure adherence rates. These include the Adherence Estimator, Adherence Starts With Knowledge (ASK)-12, ASK-20, Beliefs About Medicines Questionnaire (BMQ), Brief Adherence Rating Scale (BARS), Medication Adherence Report Scale (MARS), and Morisky Medication Adherence Scale (MMAS).

The MMAS is a quick and simple tool to use during patient encounters. Composed of four closed-ended questions about past medication use patterns, response options are “yes” or “no” (Morisky, Green, & Levine, 1986). Scoring is 1 point for a “yes” and 0 for a “no” and scores are summed. A score of 0 is considered high adherence, a score of 1–2 is medium adherence, and a score of 3–4 is low adherence. Predictive validity is 0.75 for adherence and 0.47 for nonadherence, with a sensitivity of 0.81 and specificity of 0.44. Sensitivity is a proportion of actual positives that are correctly identified as positive (e.g., the percentage of people with tuberculosis who correctly identified as having the condition). Specificity is a proportion of actual negatives that are correctly identified as negative (e.g., the percentage of people who are correctly identified as not having tuberculosis). Floor and ceiling effects are likely because of the nature of the questions, demonstrating lack of sensitivity and specificity. MMAS appears to be valid, testing true to the concept of adherence, but reliability is not high because it lacks sensitivity and specificity. A tightly controlled, randomized clinical trial on HIV medication adherence compared the MMAS, using an electronic device, and using pharmacy fill records and found that the MMAS did not perform as expected and was not an adequate measure of adherence (Holzemer et al., 2006). The MMAS may be somewhat effective at predicting risk of nonadherence but does not yet appear to be a reliable tool to measure medication adherence.

The Adherence Estimator is a brief, three-item screen for the likelihood of nonadherence for those with chronic disease (McHorney, 2009). Patients are placed into one of three categories based on the total score: low, medium, or high. Sensitivity was high (Cronbach alpha = 0.88) for accurately predicting those with medium or high risk of nonadherence, and specificity was somewhat acceptable at 59%. This tool did not measure rates of adherence to the medication. The Adherence Estimator may be useful in the clinical setting for assessing risk of nonadherence.

The 17-item BMQ is a self-report tool for assessing risk of nonadherence and adherence rates (Horne, Weinman, & Hankins, 1999). The BMQ has two sections: the BMQ-Specific, which assesses medications prescribed for personal use, and the BMQ-General, which assesses beliefs about medicines in general. The BMQ-Specific contains two five-item factors assessing beliefs about the necessity of prescribed medication and concerns based on beliefs about the danger of dependence and long-term toxicity and the disruptive effects of medication. The BMQ-General comprises two four-item factors assessing beliefs about medicine overuse and safety. The two sections can be used in combination or separately. Items are scored as follows: 1 point for “strongly disagree,” 2 points for “disagree,” 3 points for “uncertain,” 4 points for “agree,” and 5 points for “strongly agree.” Higher scores (range = 10–50) indicate better adherence. Cronbach alpha for each of the subscales is greater than 0.8 (Horne et al., 2004). The BMQ does not have the sensitivity or specificity to be used to measure OAC adherence. Although it has potential for use to predict the risk of nonadherence, the BMQ is not practical for use in the clinical setting because of the time necessary to administer and calculate results.

The ASK-20 was designed by a pharmaceutical company and identifies the risk of nonadherence (Hahn et al., 2008). ASK-20 was certified by the National Committee for Quality Assurance and consists of 20 clinically actionable items representing multiple factors affecting medication adherence. The presence of behaviors related to medication administration are noted if they occurred in the past week, month, three months, greater than three months, or never. Questions include whether the medication was taken more or less often than prescribed, skipped, or stopped. Cronbach alpha is 0.85 for the ASK-20 score, and concurrent validity in relation to self-reported adherence generally is good. The tool is not scored; therefore, a rate of adherence is not calculated. However, it may have use for assessing risk of nonadherence in the clinical setting or to stimulate a discussion with the patient about adherence.

Similarly, the ASK-12 was designed as a shorter, revised version of the ASK-20 (Matza et al., 2009). The tool includes three subscales: adherence behavior, health beliefs, and inconvenience or forgetfulness. The total score also discriminated among groups of patients who differed in self-reported adherence indicators, including whether a dose was missed in the past week, the number of days the medication was not taken as directed, and treatment satisfaction. The tool has good internal consistency reliability (Cronbach alpha = 0.75) and test-retest reliability (intraclass correlation = 0.79). Convergent validity was demonstrated through correlations with the MMAS (r = –0.74, p < 0.001) and the proportion of days covered by filled medication prescriptions in the past six months as indicated by pharmacy claims data (r = –0.2, p = 0.06). This tool may be practical for the clinical setting for predicting risk of nonadherence, as well as measuring adherence rates.
The MARS is a 10-item “yes” or “no” response instrument. The MARS was developed from the 30-item Drug Attitude Inventory and the four-item Medication Adherence Questionnaire to create a more reliable and valid tool (Fialko et al., 2008; Thompson, Kulkarni, & Sergejew, 2000; Tommelein, Mehuys, Van Tongelen, Brusselle, & Boussery, 2014). Total scores range from 0 (low likelihood of medication adherence) to 10 (high likelihood of medication adherence), reflecting adherence as a continuous variable. The development sample for the MARS showed good internal consistency (Cronbach alpha = 0.75). Three factors were identified: medication adherence behavior, attitudes toward taking medication, and negative side effects (Fialko et al., 2008). In a follow-up study, internal consistency of MARS was high (Cronbach alpha = 0.77); however, the tool correlated poorly with continuous medication refill adherence rates (r = 0.1, p = 0.01) (Tommelein et al., 2014). When lowering the nonadherence threshold stepwise from 25 to 20, MARS did not reach sufficient sensitivity (53% to 13%), specificity (57% to 94%), or positive predictive value (42% to 57%) to detect nonadherence, compared to dichotomized medication refill adherence rates. Receiver operating curve plotting, a graphical plot of true positive rate (sensitivity) and false positive rate (specificity), resulted in an area under the curve value of 0.56 (95% confidence interval [0.521, 0.616], p = 0.01); therefore, MARS does not accurately predict risk of nonadherence or rates of adherence.

The BARS is a clinician-administered medication adherence assessment (Byerly, Nakoneczny, & Rush, 2008). The BARS consists of four items: three questions and an overall visual analog rating scale to assess the proportion of doses taken by the patient in the past month. The visual analog scale serves as an additional determinant of adherence. The three questions were adapted from a lengthier adherence questionnaire used in a randomized, controlled trial, and they inquire about the patients’ knowledge of their own medication regimen and episodes of missed medication taking. The three questions pertained to (a) the number of prescribed doses taken per day, (b) the number of days, over the past month, that the patient did not take the prescribed doses, and (c) the number of days, over the past month, that the patient took less than the prescribed doses. A significant positive relationship was found between the mean BARS score and electronic monitoring (MEMS) of medication adherence (Cronbach alpha = 0.98, r = 0.59, p < 0.0001). Cronbach alpha revealed very high internal reliability (Cronbach alpha = 0.92). A moderate to strong degree of test-retest reliability also was found (Cronbach alpha = 0.53–0.92; r = 0.46–0.86). Regarding concurrent validity of the BARS, greater mean BARS adherence was significantly related to lower mean Positive and Negative Syndrome Scale total scores (Cronbach alpha = −0.4, r = −0.39, p = 0.002) and to lower mean positive symptom subscale scores (Cronbach alpha = −0.08, p = 0.01; r = −0.28, p = 0.02). Therefore, sensitivity and specificity are adequate. An initial three-month monitoring period with the BARS also demonstrated good sensitivity (73%) and specificity (74%) in identifying nonadherent patients (defined as less than 70% mean nonadherence). The BARS appears to provide valid, reliable, sensitive, and specific estimates of risk of nonadherence and adherence rates and is a promising candidate as a brief adherence assessment instrument. However, BARS has had limited use in research or clinical practice and needs additional validation.

### State of the Science

To summarize, the state of the science on assessment and measurement of OAC adherence is poor. Most measures are indirect and include a form of self-report that cannot truly capture whether the medication was taken. Although a few tools are able to assess the risk of nonadherence, they do not have the specificity to determine rates of adherence, and OAC underadherence and overadherence cannot be examined. Measures also must be sensitive enough to capture frequent and erratic occurrences of nonadherence. Many measures only have been used in research and are not practical for use in the clinical setting because they were time-consuming, costly, and impractical. A few tools demonstrated potential but need additional examination prior to recommending them for clinical use.

### Implications for Research

Additional research needs to focus on the development of multicomponent, practice-based tools to assess and measure medication adherence. Technologic approaches (e.g., apps, pill dispensers, sensors) to assess and measure medication adherence are beginning to emerge, but data on their effectiveness are limited. These tools need to incorporate the timing, dosage, frequency, and duration of the regimen to ensure that all dimensions of OAC adherence are assessed—while remaining brief and simple—to be practical in the clinical setting.

### Implications for Nursing Practice

Medication adherence is dynamic and can change from day to day, with multiple, varying factors influencing adherence rates (Gearing, Townsend, MacKenzie, & Charach, 2011). Therefore, adherence should be assessed and measured continually throughout the course of OAC treatment. Adherence also should be clearly defined prior to measurement to allow for consistent documentation in the health record. Nurses need simple and quick ways to assess and measure medication adherence.

The authors found that the MMAS and Adherence Estimator tools may be useful in predicting the risk of medication nonadherence, and the ASK-12 and BARS may be useful for measuring rates of adherence. In addition, the best time to assess for risk of nonadherence is when OAC treatment begins. Nurses can identify at-risk patients and target interventions toward those factors. This may include a discussion on the need for the medication, fitting the medication into one’s lifestyle, daily activities to enhance adherence, addressing forgetfulness, finding support for those who lack insurance, or treatment for depressive symptoms, if needed (Given, Spoelstra, & Grant, 2011). Standardized care improved adherence rates among patients with breast cancer who were prescribed tamoxifen and may improve adherence to other OACs (Grunfeld, Hunter, Sikka, & Mittal, 2005). OAC adherence is difficult to measure, but understanding when to intervene is crucial for patients at risk for poor adherence. In the fast-paced world of oncology, nurses must assess the risk for nonadherence and measure
adherence rates for all patients prescribed OACs throughout treatment and take action, working with patients to find ways to take OACs as prescribed.

References


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