Patient adherence to aromatase inhibitor treatment in the adjuvant setting

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ABSTRACT

Improvements in adjuvant systemic therapy and detection of early disease have resulted in a decline of breast cancer death rates across all patient age groups in Canada. Non-adherence to adjuvant hormonal therapy in the setting of early breast cancer may significantly affect patient outcome. Factors associated with medication adherence are complex and may be patient-related, therapy-related, and health care provider–related. To date, there is a gap in the literature concerning a comprehensive understanding of factors related to medication adherence with anti-estrogen therapy in the adjuvant setting. The literature suggests that strategies for improving adherence should focus on education of patients, assessment of the ability of patients to understand their disease and related recurrence factors, and facilitation of adherence by patients by providing adequate support and strategies for good self-management. However, more research is needed to better understand how health care providers can support women with breast cancer on oral therapy in the adjuvant setting.

KEY WORDS

Adherence, hormone receptor–positive breast cancer, adjuvant hormonal therapy, aromatase inhibitors, tamoxifen

1. INTRODUCTION

Most breast cancers (60%–70%) express the estrogen or progesterone receptor or both, and as a result, most women with hormone receptor–positive early-stage breast cancer are typically prescribed adjuvant hormonal therapy such as tamoxifen or an aromatase inhibitor (AI) for 5 or more years after definitive locoregional treatment. As a result of improvements in adjuvant systemic therapy and improved detection of early disease, breast cancer death rates have declined in all age groups in Canada since the 1990s, with survival rates in women currently being in the area of 87% [1]. However, no matter how effective a drug may be, its efficacy ultimately depends on the patient's ability to adhere to the prescribed dosing regimen in the long term.

Adherence may be defined as the extent to which patients take medications as prescribed by their health care providers [2], and it reflects both the willingness and the ability of patients to follow a prescribed treatment plan, daily and throughout the entire course of therapy. Medication non-adherence may be intentional (when a patient makes a conscious decision not to take a medication) or non-intentional (a result of forgetting or misunderstanding instructions about the dosing schedule) [3]. Thus, non-adherence may range from ceasing to take a drug to occasionally missing a dose because of forgetfulness or the complexity of fitting the dose into a daily routine [4,5]. Also, if symptoms related to the underlying disease are absent and if the patient perceives that the medication may no longer be necessary or that the perceived benefits no longer outweigh the side effects and risks experienced, then the patient may make a conscious decision not to follow the physician's recommendation in the long term [4,5].

Adherence rates are suboptimal for drugs in general, with average rates reported to be 50% for medications and even lower for lifestyle modifications such as weight loss and smoking cessation [6]. However, adherence rates for patients enrolled in clinical trials of adjuvant hormonal therapy for early breast cancer are relatively good at 72%–78% [7].

Because medication adherence may encompass a variety of decisions and behaviours, it can be a difficult parameter to accurately characterize and measure. Direct and indirect methods have both been used to assess and measure medication adherence. Direct assessment methods such as observed pill intake or measures of the drug or related markers in blood are more accurate, but they are often impractical or too expensive to implement on a large scale [5]. Indirect assessment methods include patient

self-reporting, health care provider reporting, prescription refill rates, assessment of clinical response, electronic medication monitors, and measurement of physiologic markers such as blood pressure [5]. Each of those methods has its own limitations: for example, difficulty of recall of a routine daily event such as medication-taking, distortion (in the case of self-reporting), changes in physiologic markers for other reasons, and prescription refill data not being equivalent to ingested medication and also requiring an integrated pharmacy system. Interestingly, in a study of tamoxifen adherence based on electronic monitoring, pill counts, and patient self-reporting, adherence was significantly overestimated in self-reports ($p = 0.008$) [8]. In another recent study, self-reported adherence was 100%, which did not correlate with prescription refill data [9]. Consequently, studies that use self-reported adherence data (such as most clinical trials) may over-report medication adherence.

Adherence to medication is relatively high in acute symptomatic disease states, in which the goal is cure—a visibly attainable result. However, chronic (and often asymptomatic) conditions such as hypertension, diabetes, and hyperlipidemia pose more of a problem, because the goal is long-term disease control or prevention of another medical condition. The challenges associated with long-term medication-taking are greater, the risks of undesirable medication effects are higher, the financial burden is increased, and the benefits of treatment often may not easily be evident to the patient. Thus, adherence may decline once the acute symptoms have resolved, or conversely, patients may become discouraged if the benefit is not obvious; and if the side-effects and the financial burden are undesirable, patients may therefore choose to cease taking their medication.

Cancer patients on long-term therapy are generally highly motivated to remain adherent because of the seriousness of the underlying disease and the potential risk associated with non-adherence, but suboptimal adherence has been reported in this setting. A review of studies looking at adherence to oral anti-neoplastic agents showed adherence rates ranging from 20% to 100% [10]. In a survey of 208 women on endocrine therapy for early breast cancer, in which preference for daily oral medication or monthly intramuscular injection was examined, 50% of patients admitted to forgetting or choosing not to take their current medications [11]. Similarly, in a small survey of 53 women on tamoxifen, 62% self-reported missing doses during a 6-month period, and of that 62%, 24% missed a dose 1 or more times weekly [12]. That finding is not entirely surprising because adherence to a daily oral agent for a minimum of 5 years would be challenging even for highly committed patients.

Regardless of the reasons for non-adherence, some concern is justified because a recent study showed that women on tamoxifen with an adherence rate of less than 80% (determined by prescription records) had an increased risk of mortality at a median duration of 2.4 years [13], highlighting a need for awareness of this issue and for effective strategies to improve adherence to adjuvant hormonal therapy in early breast cancer. In the present review, we discuss the current understanding of adherence to adjuvant hormonal therapy and the factors associated with non-adherence, and we present some strategies to help improve medication adherence.

2. ADHERENCE TO ADJUVANT HORMONAL THERAPY IN EARLY BREAST CANCER

2.1 Major Clinical Trials

Adherence issues during long-term oral hormonal therapy for early breast cancer have not been well studied. Much of the data comes from major clinical trials based on self-reporting by the participants. Discontinuation rates (failure to complete a 5-year course of therapy) in these trials have ranged approximately from 10% to 24% (Table I). However, the results are difficult to interpret because discontinuation rates have not always been reported in the final published analysis, and furthermore, reasons for discontinuation, when given, are not always clear.

The NCIC Clinical Trials Group MA.17 trial, which examined extended adjuvant therapy with letrozole after 5 years of tamoxifen, was one of the few trials that reported reasons for discontinuation—namely, patient refusal (11.4% letrozole; 11.1% placebo), toxicity (4.9% letrozole; 3.6% placebo), and "other reasons" (3.8% letrozole; 4.7%, placebo) [16]. The B-14 trial, which evaluated tamoxifen treatment for up to 10 years, also gave reasons for discontinuation, and interestingly, in the first 5 years, therapy discontinuation was chosen by more patients on placebo (13%) than on tamoxifen (10.2%), which suggests that medication-related adverse events are not necessarily a reason for discontinuation [14].

2.2 Non-Trial Settings

Although discontinuation rates reported in major clinical trials have generally not exceeded 25% and appear to be lower for the AIs than for tamoxifen, some studies specifically undertaken to measure adherence showed higher discontinuation rates in routine clinical practice. Most of the reports involve tamoxifen, given its longer use (compared with AIs) in this setting. In a study of 788 patient on adjuvant tamoxifen, as many as 37% either refused or stopped taking the medication within 1 year [21]. Other studies showed relatively good adherence in the first year, but a decline over time. A large study of 2378 women on 5-year tamoxifen treatment showed that overall adherence, as determined by filled prescriptions, declined from 87% in the first

TABLE I Discontinuation rates in major clinical trials of adjuvant hormonal therapy

Reference	*Trial name*	*Median duration (months)*	*Discontinuation rate (%)*		
			Tamoxifen	*Placebo*	*AI*
Fisher *et al.,* 1996 [14]	B-14	60	23	23.5	NR
Goss *et al.,* 2003 [15]	NCIC CTG	28.8	NR	9.8	9.9
Goss *et al.,* 2005 [16]	MA.17	60	NR	20.1	19.4 (letrozole)
Coombes *et al.,* 2004 [17]	IES	30.6	12.7	NR	15.5 (exemestane)
Coates *et al.,* 2007 [18]	BIG 1-98	51	11.1	NR	12.3 (letrozole)
Forbes *et al.,* 2008 [19]	ATAC	100	12	NR	13 (anastrozole)
Jones *et al.,* 2009 [20]	TEAM	33	29.5	NR	18.9 (exemestane)

NR = not reported; CTG = Clinical Trials Group; IES = Intergroup Exemestane Study; BIG = Breast International Group; ATAC = Arimidex, Tamoxifen, Alone or in Combination; TEAM = Tamoxifen Exemestane Adjuvant Multinational study.

year to 50% by year 4 [22]. Similarly, in another study of 516 women on tamoxifen, 17% stopped taking the drug within the first 2 years [23], and 31% failed to complete the 5-year course [24]. Another very large study (2816 women) reported an adherence rate of 77.9% within the first year based on prescription refill data for tamoxifen; that rate decreased to 64.8% at the end of the 3.5-year follow-up period [25].

Few data are currently available on adherence to AI therapy. In a recent comparison of 50 women on tamoxifen and an equal number on anastrozole, 80% on tamoxifen were adherent compared with 69% on anastrozole, as measured by dispensed prescriptions over a median duration of 13.6 months for tamoxifen and 16.6 months for anastrozole [9]. Patients on anastrozole were significantly older (mean: 72 years vs. 65 years for those on tamoxifen). Interestingly, self-reported adherence in both groups was 100%, underscoring the discrepancies in adherence data based on method of determination. In a very large longitudinal analysis based on filled prescriptions for anastrozole among 12,391 women with early breast cancer in 3 commercial health programs in the United States, mean adherence over the first 12 months ($n = 7132$) ranged from 82% to 88% in the 3 programs [26]. Between 19% and 28% of women had fewer than 80% of days during which medication was assessed to have been taken; they were considered to be non-adherent. For women with 36 months of continuous eligibility ($n = 999$), mean adherence rates declined over time, ranging from 78% to 86% in the first year, and reaching 62%–79% by year 3. In a Canadian longitudinal drug utilization database (data not shown), which tracked prescription purchases claimed through insurance plans by 6527 people who filled prescriptions for an oral hormonal breast cancer drug from September 2005 to April 2007 (1985 on anastrozole, 640 on exemestane, 1414 on letrozole, and 2488 on tamoxifen), prescriptions continued to be filled after 1 year by significantly more patients on anastrozole (72.2%) than on tamoxifen (67.2%), letrozole (58.8%), or exemestane (55.0%, $p < 0.0001$).

A number of trials assessing adherence to AIs are either in progress or recruiting, and the results of those trials should provide valuable information on patterns of adherence to AI adjuvant therapy.

3. FACTORS AFFECTING ADHERENCE TO ADJUVANT ENDOCRINE THERAPY

Patient-related, therapy-related, or health care system–associated factors may affect adherence (Table II) [27], and non-adherence is usually a result of a combination of these factors. Studies on long-term antiretroviral therapy for HIV show that a balance between perceived necessity for treatment and concerns about adverse effects predicts subsequent adherence [28]. To identify patients who are likely to be non-adherent and who may benefit from more careful monitoring and support, recognition of the factors associated with lower adherence is important.

Some patient-related factors, such as remembering to take the medication, are directly under the patient's control; others are inherent. Age has been identified as one of the key factors associated with lower adherence rates, and older age groups (>75 years) and younger age groups (<45 years) have both been significantly associated with non-adherence [3,21,22,25,29,30]. Of 961 women 65 years of age or older, 49% discontinued tamoxifen before the end of a 5-year administration period, and those who discontinued the drug were more likely to be 75 years of age

TABLE II Factors affecting compliance to adjuvant endocrine therapy

Patient-related factors	*Treatment-related factors*	*Health care provider–related factors*
Remembering to take medication (older and younger age groups associated with non-adherence)	Drug adverse effects	Importance of adherence may not be emphasized
Depression	Side effects may be underestimated by physician	Potential difficulties of long-term adherence may not be discussed
Antidepressant use	Unexpected effects associated with non-adherence	Lack of patient support in dealing with side effects
Mastectomy		Patient may not be satisfied with health care provider
Lack of belief in treatment		
Poor awareness of therapeutic benefit		
Inconvenience		
Difficulty swallowing pills		

or older [29]. Other studies support that finding [22,25,30]. At the other end of the spectrum, a study on adjuvant tamoxifen found that non-adherence (37% within the first year) was significantly associated with younger age ($p < 0.001$) [21], a finding that has also been demonstrated in other studies [22,25]. Non-adherence among the elderly has been suggested to possibly be a result of psychosocial issues such as memory problems and decreased social support [22]. Lesser adherence among younger women has been hypothesized by some authors to be related to their having less of a sense of vulnerability, being less willing to accept the side effects of tamoxifen use, or simply being unaccustomed to taking medications and thus being more likely to forget [3,22,25]. These hypotheses have not been extensively studied.

Other patient-related factors that have been associated with non-adherence are antidepressant use and mastectomy [21,22,25]. Depression has been noted as a risk factor for non-adherence to medications [31]. Why mastectomy is associated with non-adherence is not clear, but we hypothesize that women who have had this type of surgery may perceive this approach as being more aggressive than lumpectomy; they may thus rationalize that they do not require ongoing therapy, or compared with women who have had a lumpectomy, they may be less willing to tolerate medication side effects. Although most patients typically report unintentional non-adherence (that is, forgetting to take their medication), a small study of 131 patients on breast cancer drugs showed that 16.7% of those who were non-adherent intentionally chose not to take their medication [3]. In that study, patients who reported deliberately missing their medication viewed themselves as having less influence over their own health than did those who forgot. Other reasons that have been suggested to contribute to non-adherence are poor awareness of the therapeutic benefit and lack of belief in the treatment [7,27]. Aspects of medication-taking disliked by patients, such as difficulty swallowing pills or inconvenience, have also been associated with non-adherence [3].

Drug side effects can contribute to a patient's decision to cease medication, particularly if the patient is unprepared for the side effects or is not educated in how to manage them. In a study of 881 women on adjuvant tamoxifen, adherence was significantly lower among women who experienced side effects about which they had not been informed in advance than among women who had been informed about possible side effects (62% vs. 85%, $p < 0.0001$) [30]. Physicians may underestimate side effects or may selectively mention only side effects for which they are likely to see difficulties [32].

Reports examining conversations between oncologists and women starting adjuvant hormonal therapy indicate that some oncologists display a lack of urgency in their conversational framework on adjuvant treatment than on other treatments such as adjuvant chemotherapy [33,34]. The topic of adherence may be omitted or not specifically addressed in discussions between the oncologist and the patient during the initial and follow-up visits. An observational study of visits between 28 postmenopausal early-stage breast cancer patients and their oncologists showed that discussions of medication persistence (the extent to which patients take medications as prescribed by their health care providers) were often based on study data and not linked to the patient or to how the study data related to her situation; and furthermore, the potential difficulties in remaining adherent were not addressed [34]. Thus, the importance of adherence may not be fully appreciated by the patient, resulting in decreased motivation to remain adherent. Good communication between the patient and the health care provider is crucial, because dissatisfaction with the treating physician has been shown to correlate with non-adherence [35]. Furthermore, provider input and support have been found to affect adherence. In a study of women on tamoxifen, the rate of continued use 4 years after initiation was higher among women who reported receiving what they considered to be the right amount of support from physicians and other health professional professionals than among those

who reported more or less support than needed [30]. In that study, women who also reported that the doctor had made the decision about tamoxifen initiation (with or without patient input) were more likely to continue with treatment than were women who had made the decision on their own. Thus, adherence is a complex issue not only requiring an effective relationship between the patient and health care provider, but also likely involving individual behavioural traits of various types of patients.

The contribution of socioeconomic factors to medication adherence has not been well studied. It is possible that the cost of medication may also be a contributing factor to non-adherence in some settings, given the greater cost of the AIs (approximately 10 times the cost of tamoxifen). Although some factors that contribute to non-adherence to oral therapy have been identified in women with breast cancer, it is still not clear why some women adhere to therapy and others do not, or why some fail to persist over time. This gap in understanding limits the ability to fully define strategies that might be used to help support such patients. Further research in this area is needed.

4. STRATEGIES FOR IMPROVING ADHERENCE TO LONG-TERM THERAPIES

Recognizing the importance of adherence in long-term therapies for chronic diseases, the World Health Organization published a strategy report in 2003 [36]. Although the breast cancer population was not specifically discussed in the report, the key messages are still relevant. It was noted that the tendency is to focus on patient-related factors as the cause of problems with adherence, but that adherence is simultaneously influenced by several factors, including the health care team and social and economic factors. Furthermore, no single intervention strategy, or combination of strategies, has been shown to be effective across all patients, conditions, and settings. Based on research in the behavioural sciences, it was suggested that patient populations be segmented according to their level of readiness to follow health recommendations—that is, health care providers should be able to assess the patient's readiness to adhere, to provide advice on how to adhere, and to follow the patient's progress at every contact. It was recognized that health care providers can have a significant effect by assessing the risk of non-adherence and by delivering interventions to optimize adherence.

An analysis of randomized controlled trials to assess interventions to help patients adhere to long-term treatments showed that such interventions are complex and involve combinations of more convenient care, information, reminders, self-monitoring, reinforcement counselling, family therapy, and other forms of additional supervision by a health care provider [37]. Such interventions are potentially applicable to patients on adjuvant therapy for breast cancer and would involve educating those patients on the importance of persistence with medication, ensuring that each patient has adequate support to remain adherent, and making all patients aware of self-management programs (Table III).

4.1 Patient Education

Detailed, in-depth interviews of a small group of patients with a variety of chronic conditions requiring long-term medication showed that a key factor in adherence was whether the patients could "make sense" of their medication-taking and, further, how they interpreted the data they gathered from their medication experience. Both factors influenced their medication-taking practices [38].

"Making sense" of medication-taking was an ongoing process and had a bearing on self-regulated medication-taking, which was not necessarily discussed with the health care provider. That study also found that some patients went into a "stunned mode," often at the beginning of their diagnosis, that prevented them from making sense of their illness. The patient's ability to make sense of the gravity of their illness is influenced by a variety of contextual factors, such as patient knowledge, value system, beliefs, trust in the health care provider and in the system, emotional state, cognitive ability, and stress [38]. Helping the patient to understand and make sense of the illness and being aware of whether the patient is in a psychological state to remember information are key goals of the health care provider. Potential side effects and management strategies should be discussed, and written information on potential benefits and risks about the treatment should be provided [39]. Visual decision aids, such as illustrative graphs of the absolute risk reductions expected with the use of adjuvant hormonal therapy in early-stage breast cancer, can be used to reinforce the important benefits of therapy and to involve patients more intimately in their own decision-making [40,41].

TABLE III Strategies for improving adherence

Patient education
Assess the patient's ability to make sense of medication-taking.
Discuss side effects.
Provide written information about treatment.
Patient support
Manage drug side effects.
Ensure accessibility to health care professionals.
Provide contact information so that the patient can communicate any concerns.
Provide information about support groups.
Monitor patient and provide feedback.
Self-management programs
Supply or suggest pill boxes to organize daily doses.

4.2 Patient Support

Ensuring accessibility to health-care professionals—for example, convenient scheduling of follow-up appointments and access to ancillary caregivers such as nurses, pharmacists, behavioural specialists, and so on—is important [27]. Providing the patient with contact information so that they can ask about any concerns and providing information about support groups and organizations might be useful [39]. Frequent monitoring of the patient and provision of feedback can improve adherence, [42] and in that context, the family physician can have an important role in supporting patients on treatment. Drug side effects or depression can also be appropriately managed by the family physician. In some cases, non-adherence may arise unintentionally—for example, if the patient is undergoing surgery or treatment for another unrelated condition [43]—and again, the family physician can ensure there is no confusion about how to deal with multiple medications. Oncology nurses also have an important role in identifying non-adherent patients by tailoring interventions to individuals and by motivating patients to strive for successful outcomes of their endocrine therapy [39].

5. SUMMARY

Non-adherence to adjuvant hormonal therapy in the setting of early breast cancer may have a significant effect on patient outcome. Although discontinuation rates for adjuvant hormonal therapy in major clinical trials have generally not exceeded 25%, specific studies on adherence to adjuvant therapy in the non-trial setting have shown higher discontinuation rates, with increases over time. Factors associated with medication adherence are complex and may be patient-related, therapy-related, and health care provider–related. Patient-related factors are complex and encompass not only the patient's understanding of the disease, but also their emotional state and their value system and beliefs. Health care providers may also underestimate such factors in the clinical setting and may not always address issues of adherence with their patients, thus undermining its importance. To date, there is a gap in the literature on the subject of a comprehensive understanding of factors related to medication adherence with hormonal therapy in the adjuvant setting. The literature suggests that strategies for improving adherence should focus on educating the patient, assessing the patient's ability to make sense of the disease, facilitating adherence by providing adequate support, and providing strategies for good patient self-management. However, more research is needed to better understand how health care providers can support women with breast cancer on oral therapy in the adjuvant setting.

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