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Adherence to endocrine therapy in breast cancer adjuvant and prevention settings

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Abstract

Background—Adherence to oral endocrine therapy in adjuvant breast cancer settings is a substantial clinical problem.

Methods—To provide current perspective on adherence to oral endocrine therapies, a comprehensive literature review was conducted.

Results—In adjuvant trials, endocrine therapy adherence is relatively high with greater adherence for aromatase inhibitors compared to tamoxifen. In contrast, adherence to adjuvant therapy in clinical practice is relatively poor, with only about 50% of women successfully completing five years therapy. Importantly, good adherence (> 80% use), has been associated with lower recurrence risk. Endocrine therapy adherence in primary breast cancer prevention trials parallels that seen in adjuvant trials. Factors associated with non-adherence include low recurrence risk perception, side effects, age extremes, medication cost, suboptimal patient-physician communication, and lack of social support. Few prospective studies have evaluated interventions designed to improve adherence. Interventions currently proposed reflect inferences from clinical trial procedures where clinical contacts are commonly greater than in usual practice settings.

Conclusions—For optimal breast cancer outcome, adherence to endocrine therapy must improve. While general recommendations likely to improve adherence can be made based on clinical trial results and preliminary prospective trial findings, research specifically targeting this issue is needed to establish effective intervention strategies.

Adherence to oral endocrine therapy for adjuvant breast cancer treatment and for breast cancer prevention are substantial problems for clinicians and healthcare systems (1, 2, 3). In the adjuvant setting, adherence to endocrine therapy now takes on greater importance given reports that adjuvant tamoxifen of greater than five years duration is associated with lower recurrence risk (4, 5).

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Adherence is defined as a composite of compliance (how well physician's orders are followed) and persistence (how long an individual continues on prescribed therapy) (6). Currently no gold standard method exists for adherence measurement. Adherence can be estimated from prescription and medical claims and pharmacy databases, medical record review, hospital databases, pill counts, patient self-reports, prospective studies, and, rarely, pharmacologic assessments of drug concentrations. Methodological concerns were raised by a study of 242 patients where correlations of only 0.2 to 0.4 was seen comparing endocrine therapy adherence estimates from self-report, physician rating, refill records, and anastrozole concentrations (7). Other studies found breast cancer patients overestimated adherence to tamoxifen based on prescription checks (8) or microelectronic monitoring (9). In this regard, in a report comparing non-adherence to adjuvant anastrozole using three separate databases in the same population, estimates of non-adherence varied from 32% to 50% (10); however, subjects in these databases had variable medical insurance coverage which may partially explain adherence differences. Despite these concerns, consistent general conclusions have emerged from studies using various methods of adherence assessment.

Adjuvant endocrine therapy adherence in clinical trials and clinical practice

Clinical adjuvant endocrine therapy trials, where adherence is commonly closely monitored, did not suggest a major adherence problem. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial in breast cancer patients receiving adjuvant tamoxifen or placebo, discontinuation rates were 23% in both groups at 60 months median follow-up (11). In the NSABP B-24 adjuvant intraductal breast cancer trial, 60 month discontinuation rates for placebo were 30% compared to 33% for tamoxifen (12).

The seminal reports by Partridge and colleagues (1, 2) brought attention to the issue of poor adjuvant tamoxifen adherence in clinical practices. In a retrospective analysis of prescription claims (Medicaid and Pharmaceutical Assistance to Aged and Disabled [PAAD]) databases from the years 1990 to 1996, adherence to adjuvant tamoxifen was 83% after one year, 68% after two years, 61% after three years, and only 50% after four years. Other studies also found that more than half of breast cancer patients discontinue endocrine therapy prior to completion of a recommended five-year treatment (13, 14). For aromatase inhibitors, the commonly experienced arthralgias raise particular adherence concerns (15, 16, 17). However, in several adjuvant clinical trials, adherence to aromatase inhibitors was closely comparable, or even superior to tamoxifen. In the Arimidex, Tamoxifen, Alone and Combined (ATAC) trial after five years, 2.1% of the anastrozole-treated patients and 14.3% of the tamoxifen-treated patients had discontinued use due to adverse events (18). Similar adherence was seen in both treatment groups in adjuvant trials comparing the aromatase inhibitor, exemestane, to tamoxifen (14% discontinued therapy in both arms) (19) and the aromatase inhibitor, letrozole, to placebo (only 10% discontinued therapy in both arms) (20).

Recent systematic reviews on adherence and/or persistence to adjuvant endocrine therapy in clinical practice settings identified 29 reports. Adherence in tamoxifen users ranged from 41% to 88%. While adherence in aromatase inhibitor users ranged from 50% to 91% (21). These findings were extended by Huiart and colleagues (22) who conducted meta-regression analyses to provide summary estimates of non-persistence in 17 trials. For tamoxifen,

5-year nonpersistence was 47.2% (95% CI 41.1%–53.5%) compared to 31.0% (95% CI 25.9–37.5%) for aromatase inhibitors (Table 1).

The findings are somewhat mixed considering aromatase inhibitor adherence in clinical practices (23, 24); however, in the United Kingdom (UK) general practice database, the one year discontinuation rate for adjuvant aromatase inhibitor use was 5% compared to about 10% for tamoxifen in women > 49 years old and 20% for tamoxifen in women < 40 years old (25). Similarly, in the Disease Analyses database (IMS Health, Germany), among 16,865 breast cancer patients, 3 year discontinuation rates were 52% for tamoxifen, 47% for anastrozole and 44% for letrozole (26). A randomized adjuvant adherence trial found shorter time to treatment discontinuation for exemestane, compared to letrozole (HR 1.5, 95% CI 1.1–2.1) (27).

In summary, a substantial problem regarding adherence and persistence to adjuvant endocrine therapy remains in clinical practice. Somewhat surprisingly, adherence to aromatase inhibitors has been similar or superior to adherence to tamoxifen in several settings.

Adjuvant endocrine therapy adherence and clinical outcome

Evidence that adherence to adjuvant endocrine therapy could influence clinical outcomes came from a series of randomized adjuvant breast cancer trials evaluating duration of tamoxifen use. As summarized In Early Breast Cancer Trialist Cooperative Group (EBCTCG) analyses, compared to no therapy/placebo, with tamoxifen for one year, reduction was 27% for 2 years, reduction was 33%; and for 5 years, reduction was 47%, P trend < 0.00001(28).

Adherence to adjuvant tamoxifen therapy and breast cancer outcome has been examined in several cohort studies. In a U.S. cohort of 1,837 older women with early-stage breast cancer, those who used tamoxifen less than one year had substantially higher breast cancer mortality than those who used the drug for five or more years (HR 6.26, 95% CI 3.10–12.64) (29). Similar findings were reported from a Scottish cohort of 2,080 early-stage breast cancer patients. In that study, tamoxifen adherence < 80% was associated with increased mortality (HR 1.100, 95% CI 1.001–1.21) (30).

In the managed care Kaiser Permanente Northern California population, among 8,769 breast cancer patients, 2,761 (31%) discontinued therapy within 6 months of diagnosis (based on automated pharmacy records); of those who continued, 1,684 (28%) were non-adherent (possession ratios <80%; defined as days with index prescription supplies/total days of follow-up). The survival at 10 years was 80.7% and 73.6% for those who continued therapy compared to those who discontinued therapy, respectively (P < 0.001) (31). Of those who continued therapy, survival was 81.7% in those adherent to therapy, compared to 73.6% in those non-adherent. In a similar study in Kaiser Permanente Southern California, although breast cancer recurrence was lowest in women with greater adherence (possession ratios >80%), the rates were not markedly different from women with less regular use (32). In a retrospective cohort study of 3,361 Scottish breast cancer patients, low adherence of < 80%

to adjuvant tamoxifen in aromatase inhibitor was associated with poor survival (HR 1.20 95% CI 1.03–1.40, p = 0.019) (33).

In a prospective cohort of 417 localized breast cancer patients in Sweden, non-adherence at one year was associated with increased early breast cancer events (HR 2.97,95% CI 1.08–8.15) (34). In a study with 857 low-income women with early breast cancer, more recurrences and cancer-deaths were observed in women non-adherent to endocrine therapy, but the results were not statistically significant (35). Similarly, in a study of 690 women International Breast Cancer Study Group trials 13–39 and 14–93, those with ≥ 4 years SERM use had longer disease-free survival compared to those with < 4 year use (71% vs. 64%, HR 1.31, 95% CI 0.86–1.98, p = 0.20) (36) (Table 2). In a small study of 116 men with breast cancer overall survival was greater in those adherent to tamoxifen adjuvant therapy (37).

Thus, lack of adherence and persistence to prescribed endocrine adjuvant therapy represents a barrier to achieving favorable outcomes for breast cancer patients. The magnitude of the benefit of being adherent to adjuvant endocrine therapy is comparable to that seen with the addition of adjuvant chemotherapy.

Adjuvant endocrine therapy adherence and the oncologist

Emerging data suggests that a substantial proportion of women who qualify for adjuvant endocrine therapy are not receiving this intervention. In a population of 13,753 early stage hormone-receptor positive breast cancer patients in the managed care Kaiser Permanente Northern California group, studied within one area year of diagnosis, 30% of women did not initiate endocrine adjuvant therapy defined as having < 2 prescriptions for tamoxifen or aromatase inhibitor filled within the first year after the cancer diagnosis (38). In the Kaiser Permanente Southern California population of breast cancer survivors, nearly 24% (3,237/13,412) of patients with estrogen receptor positive disease did not use endocrine therapy (or had discontinued treatment within six months) despite having pharmacy coverage (32). This finding stimulated that organization to implement a medication adherence tool in the electronic medical records to potentially improve adherence. In the Women's Health Initiative cohort, in 3,588 patients with hormone receptor positive, early-stage invasive breast cancer evaluated within five years of diagnosis by survey questionnaire, while adjuvant endocrine therapy use was reported by 83%,17% reported no use. In their response, women cited "lack of physician recommendation" as the most common reason for non-use. (39). Finally, 743 patients, identified from SEER registries, eligible for adjuvant endocrine therapy were surveyed four years after diagnosis, surprisingly 10.8% never initiated therapy, and 15.1% started therapy but discontinued before four years (40) (Table 3). While detailed information on the characteristics of those not initiating adjuvant endocrine therapy are not currently available, further exploration of this issue is warranted.

Data is sparse regarding the communication between oncologists and breast cancer patients on their therapeutic plan, as it is difficult to conduct linguistic communication studies. However, one study videotaped the initial breast cancer adjuvant therapy discussion in a series of 28 early stage patients and found the issue of adherence to be poorly addressed.

Much of the discussions on endocrine therapy focused on side effects and trial findings rather than on the importance of adherence (41).

Finally, a recent study found substantial discordance in adherence to adjuvant endocrine therapy when comparing results among prescription refill information, patient self-report, and oncologists' estimates. The oncologists estimated their patient's adherence at over 94% which was less than estimated by telephone questionnaire self-report (P=0.003), or by the pharmacy database where only 67% of women > 65 years old were identified as having drug available (P=0.0001) (42).

Adjuvant endocrine therapy adherence in long-duration clinical trials

Interest in adherence to long-term adjuvant endocrine therapy regimen was enhanced by the recent report from the worldwide Adjuvant Tamoxifen Longer Against Shorter (ATLAS) adjuvant trial where continued tamoxifen use for longer than five years reduced breast cancer recurrence (P= 0.002) and overall mortality (P= 0.01) (4). Based on self-report, five year adherence was an excellent 84% for continued tamoxifen users. In contrast, the Investigation on the Duration of Extended Adjuvant Letrozole treatment (IDEAL) trial entered 1,250 early breast cancer patients comparing 2.5 years to 5 years of extended letrozole use after 5 years of adjuvant endocrine therapy found overall non-adherence was 18.4% at 2.5 years (43). It is not clear whether this apparent difference between long term continued tamoxifen and continued aromatase inhibitor use represents real differences in tolerability, or are the result of the limited data on the aromatase inhibitors currently available. In any event, more information is needed regarding persistence to long-term aromatase inhibitor adjuvant use.

Endocrine therapy adherence in breast cancer prevention trials

Available evidence suggests that adherence to endocrine therapy in primary breast cancer prevention trial participants is similar to that seen in the adjuvant setting. In the NSABP P-1 prevention trial, discontinuation rates after 54.6 months mean follow-up were 23.7% on tamoxifen, and 19.7% on placebo (11). Discontinuation rates were somewhat higher in the International Breast Intervention Study-1(IBIS-1) where, in a primary prevention setting, the 50 month median follow-up discontinuation rate for tamoxifen was 36% compared to 26% for placebo (44). In the longer intervention duration Royal Marsden Hospital trial comparing tamoxifen to placebo, therapy was prematurely discontinued at a median of 70 months in 46% of tamoxifen and 36% of placebo participants, respectively (45). In the NSABP STAR prevention trial, 5-year adherence was 70.8% for tamoxifen and 73.9% for raloxifene ($p < 0.001$) (46).

The aromatase inhibitor, exemestane, has been compared to placebo for primary breast cancer prevention in the Mammary Prevention (MAP).3 trial. After median 35 months follow-up, a 65%, statistically significant, relative reduction in invasive breast cancer incidence was seen for exemestane (47). During the study, exemestane was discontinued because of "intolerable side effects" by 15.4% of participants but surprisingly, 10.8% of placebo participants discontinued study pills for the same reason. With only a net 5.3%

difference, a major influence of factors other than drug side effects likely influenced the adherence results seen. A similar result was seen in the MA.17 adjuvant trial, where about 20% of breast cancer patients in the placebo group reported climactic symptoms (48). These results point to the importance of placebo controls to generate the most reliable tolerability information.

In a prevention study, adherence was related to outcome in the Women's Health Initiative (WHI) trial of estrogen alone. In this study, when 10,739 postmenopausal women with prior hysterectomy were randomized to conjugated equine estrogen alone or placebo, surprisingly, a statistically significant, lower breast cancer incidence was seen in the estrogen alone group in intent-to-treat analyses (HR 0.77, 95% CI 0.62–0.95) (49). However, in sensitivity analyses, censoring participants with less than 80% adherence to the pill taking regimen, an even stronger association between estrogen alone use and lower breast cancer incidence was seen (HR 0.68, 95% CI 0.49–0.95).

Factors associated with non-adherence to endocrine therapy in breast cancer prevention trials

Factors predictive of tamoxifen chemoprevention non-adherence were examined in the P-1 breast cancer prevention trial. Current smokers and heavy alcohol users had lower tamoxifen adherence while obesity and lower physical activity were unrelated to adherence (50). Similar findings were seen in 100 participants in the IBIS-1 study where women with smoking history also were less likely to persist with their randomized drug (51). In addition, in the IBIS-1 trial, use of additional prescribed medication was an important factor in predicting successful completion of therapy ($P = 0.04$) (51). The latter findings suggest that women already using other prescription medications may represent a potentially favorable population, and thus, be more likely to accept and adhere to endocrine chemoprevention regimens. Lack of influence of obesity and low physical activity on adherence suggests factors other than an unhealthy lifestyle are related to medication discontinuation.

Endocrine therapy for prevention in clinical practice

Currently, use of the two drugs approved for chemoprevention in the US (tamoxifen and raloxifene) continues to be low (52), and, for this reason, information on adherence in clinical practice settings is not available. However, a review of a clinical experience from the Partners HealthCare System identified 2,938 women with breast lesions with atypia. Women who received no chemoprevention had 10 year breast cancer incidence of 21.3% compared to 7.5% ($p<0.001$) in women who did receive chemoprevention (53).

Factors associated with non-adherence to adjuvant endocrine therapy

Factors associated with non-adherence to adjuvant hormonal therapy include lack of physician recommendation (32), patient perception of low risk for recurrence (54), adverse effects of therapy (55, 56, 57), age extremes: older age (23, 58), and younger age (23, 59), medication costs (60, 61, 62), low social economic status (63), sub-optimal patient-physician communication (64), higher co-morbidity (23, 59, 62), cigarette smoking (50, 51) and

lack of social support (65) (Table 4). Similar factors were associated with adherence in a low-income population in California (66). Findings regarding adherence by race/ethnicity have produced mixed results (23, 38, 67).

Many oncologists likely consider endocrine therapy side effects to be a major factor influencing therapy adherence. However, the available evidence identifies a less straight forward relationship. In breast cancer patients in the Commonly used Medications and Breast Cancer outcomes (COMBO) study, among 538 participants, 18.2% discontinued use before completing 5 years of therapy, while 25% of discontinued after < 1 years use (68). As in several prior reports, women who discontinued therapy were more likely to have been tamoxifen (43.9%) compared to aromatase inhibitor users (22.4%). Of interest, the only adverse effect significantly associated with discontinuation of both aromatase inhibitor and tamoxifen was headaches, an adverse event not commonly associated with these therapies. Such findings suggest, that while control of adverse effects is an important clinical consideration, adverse effects of endocrine therapy use may not play a major role in determining adherence and persistence to adjuvant endocrine therapy.

Factors adversely influencing adherence, perhaps in unexpected ways, are anxiety and depression. Following a breast cancer diagnosis, anxiety and depression decreases from about 50% in year one to about 15% in year five (69), a reciprocal to endocrine therapy adherence over the same period (1, 3, 70) (Figure 1). Supporting the concept that greater patient anxiety correlates with better adjuvant hormone therapy adherence are findings from the prospective COMPAS study where breast cancer patients with higher anxiety levels had better adherence to adjuvant endocrine therapy (P= 0.028) (71). In an extremely large breast cancer population from IMS HEALTH, Germany with 17,512 patients, depression ($p < 0.002$) was also associated with decreased risk of treatment discontinuation (26). As anxiety and depression can be linked in a cancer population, unraveling the relative contribution of these two factors on adjuvant endocrine therapy adherence requires further study. In this regard, despite early concerns, evidence from the NSABP placebo-controlled clinical prevention trial found depression was not increased by tamoxifen use (72, 73).

Clinical trials to improve endocrine therapy adherence

Few prospective studies have evaluated interventions designed to improve adherence to endocrine adjuvant therapy. However, to guide future study designs, theoretical models of factors influencing adherence and persistence have been proposed (74).

While adherence to endocrine therapy in breast cancer adjuvant and prevention settings remains problematic, there are limitations to the currently available information. As reviewed (59, 75), only modest information about factors associated with continued hormone therapy use are known and, importantly, few of the factors identified are easily modifiable. In addition, current medical claims databases, commonly used in adherence analyses, contain limited information on healthcare practice patterns or patient characteristics needed to identify new potentially modifiable factors.

Despite the important influence of adjuvant endocrine therapy adherence on clinical outcome, there has only been one full scale, randomized intervention trial designed to improve adherence completed to date. The Patient's Anastrozole Compliance to Therapy (PACT) program was a randomized, prospective, multicenter study designed to improve persistence and compliance to adjuvant endocrine therapy (76). In this trial, 4,844 patients were randomly assigned to standard therapy or standard therapy plus mailed educational materials (EM) including monthly reminders on persistence and additional letters and brochures. Questionnaires were completed before therapy was initiated, at 12 and 24 months and at treatment discontinuation. At one year, there was no difference in the primary endpoint of compliance (88.5% vs. 88.8 %, respectively, $p = 0.81$). Thus, provision of education materials did not increase adherence to adjuvant endocrine therapy (76).

A more promising result was seen in a smaller COMPAS study of 181 patients receiving adjuvant aromatase inhibitor therapy. The randomization was either to a control condition, a letter group where participants received 5 mailings in the first year and 3 in the second, and a telephone group where participants were contacted by a study nurse using a semi-structured interview technique at the same intervals as in the letter group (77). Adherence was determined as a composite of self-report using a standardized questionnaire plus medication possession ratios calculated from pharmacy prescription refill information. At 12 months, 48% in the control group, 63% in the telephone group, and 65% in the letter group were judged adherent. While the differences between the groups were not statistically significant, a post hoc analysis pooling both interventions versus control indicated a significant difference favoring intervention ($p=0.039$). These encouraging results provide a foundation for a future confirmation trial as either intervention would be feasible for implementation in clinical practice settings.

Focus on endocrine therapy patient education: "Optimization of expectations"

There is emerging evidence that a patient's expectation regarding the benefits and drawbacks of a therapy can influence of adverse and persistence with therapy. A meta-analysis identified significant associations between cancer patient's expectation of developing adverse effects and the actual adverse effect experience (78). When 597 early stage breast cancer patients prescribed tamoxifen were followed for two years, 17% discontinued tamoxifen use. Of these, women with neutral or negative beliefs about tamoxifen efficacy were significantly more likely to discontinue than those with more positive beliefs. Based on these and similar findings, several strategies to enhance endocrine therapy adherence are now focused on the development and testing of structured educational sessions implementing at the beginning of therapy with the goal of optimization of expectations. In another study, the balance between efficacy and side effects was assessed in women receiving adjuvant endocrine therapy with an Adaptive Conjoint Analysis (ACA) customized to each patient. Using such information, a benefit/drawback ratio was calculated and the 16% of women who valued the efficacy less than the adverse effects had substantially lower adherence (79). Based on such findings, an ongoing randomized, controlled trial is

evaluating a three session program of cognitive, behavioral training designed to provide a realistic and balanced view of endocrine therapy (80).

Recommendations for improving adherence and clinical practice

Despite the paucity of full scale clinical trial evidence, there are strategies for implementation in current clinical practice which would likely have a favorable effect on endocrine therapy adherence resulting in more favorable clinical outcome.

Adherence to endocrine adjuvant therapy has been higher in clinical trials where patient contacts are commonly greater than in clinical practice settings, and where concerned attention is directed at encouraging the maintenance of adherence. Strategies to increase patient contacts which incorporate emerging technologies such as email reminder programs and use of cell phone apps (81, 82, 83, 84) shown to improve adherence in other disease settings, seem promising to evaluate in breast cancer trials. Strategies to increase contacts with patients in practice settings include use of automated telephone refill reminders and implementing medication adherence tools in electronic medical records. The concept that increased contacts with patients would increase endocrine therapy adherence is strengthened by the findings from the COMPAS trial where both additional mailings and telephone contacts seem to influence favorable adherence (77).

While a waiting results of ongoing clinical studies, one could reasonably conclude that attention to endocrine therapy patient education to optimize realistic patient expectations for adjuvant endocrine therapy, besides being good medical practice, also could improve therapy adherence. For infusional chemotherapy, in many practices, the benefits and risks of therapy, originally discussed by the oncologist, are reinforced in formal chemotherapy education sessions by a mid-level provider. A similar approach to improve adjuvant endocrine therapy patient education could be considered. Educational interventions should focus on increasing patient’s understanding of the benefits and risks of therapy including the relationship between therapy adherence and persistence and higher efficacy of the therapy in reducing cancer recurrence. Implementation of these recommendations is likely to favorably impact adherence in clinical practice at this time. More definitive evidence must come from future activity in the research arena.

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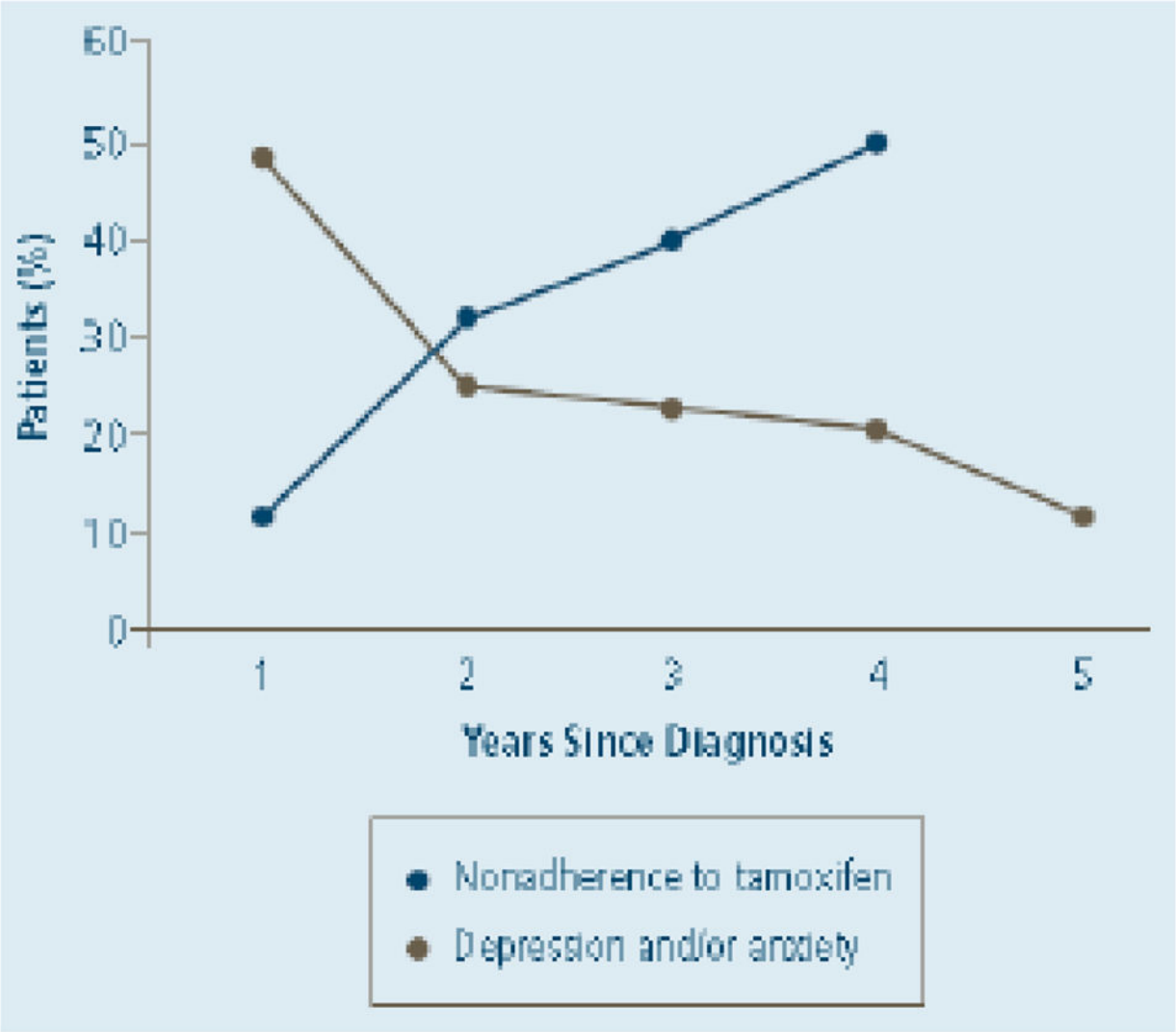

Figure 1.
Non-adherence Rates for Adjuvant Tamoxifen Therapy in Clinical Practice and Incidence of Depression and/or Anxiety

Table 1

Systematic Reviews of Adherence to Adjuvant Endocrine Therapy

	Tamoxifen	Aromatase inhibitor
Adherence (range)[1,2]	41% to 88%	52% to 91%
Therapy discontinuation (range)[1]	15% to 20% within year 1	5% to 25% within 2 years
5 year therapy discontinuation from meta-regression analysis[2]	47.2% (95% CI, 41.1% to 53.5%)0	31.0% (95% CI, 25.9 % to 37.5%)

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Table 2

Studies Relating Duration of and/or Adherence to Adjuvant Endocrine Therapy to Breast Cancer Outcome

Lead Author	Study	Findings
EBCTCG – Early Breast Cancer Trialist Collaborative Group 2001	Overview analyses of randomized clinical trials evaluating duration of tamoxifen use	Tamoxifen duration 1 year, recurrence reduced 27%; tamoxifen duration 2 years, recurrence reduced 33%; tamoxifen duration 5 years, recurrence reduced 47%; P=trend < 0.00001
Yood 2008	Cohort of 1,837 US early stage breast cancer patients ≥ 65 years old	Adjuvant tamoxifen < 1 year vs. ≥ 5 years with higher breast cancer mortality (HR 6.26, 95% CI: 3.10–12.64)
McCowan 2008	Resospective cohort of 2080 Scotish early stage breast cancer patients	Adherence to tamoxifen < 80% associated with poorer survival (HR 1.10, 95% CI: 1.001–1.21)
Hershman 2010	Northern California Kaiser Permanente cohort of 8769 women with early stage, hormone-sensitive breast cancer and endocrine therapy adherence (drug availability)	31% discontinued therapy, 10 years survival was 73.6% 69% continued therapy, 10 year survival was 80.7%; P<0.001
Xu 2012	Cohort of 116 men with early stage, hormone sensitive breast cancer and hormone therapy adherence	For those adherent, 10 year survival was 79.6%; For those non-adherent, 10 year survival was 50.5%, P=0.008
Markula 2012	Prospective cohort of 417 patients with early stage breast cancer Sweden and adherence (self-report) to adjuvant endocrine therapy	Non-adherence at the 1-year visit associated with increased early breast cancer events HR 2.97, 95% CI 1.08–8.15
Haque 2012	Southern California Kaiser Permanente cohort of 22,850 women with early stage breast cancer and endocrine therapy adherence (drug availability)	Women with high adherence had greater recurrence risk reduction (e.g., HR=0.42, 95% CI: 0.36–0.47 for tamoxifen) compared to those with less adherence (HR=0.46, 95% CI: 0.41–0.52 for tamoxifen) but the difference was not statistically significant.
Pagani 2013	International Breast Cancer Study Group trials 13–93 and 14–93 with 690 women with early stage breast cancer or SERM's	Women with ≥ 4 years of SERM had longer 10-year disease-free survival (71%) compared to < 4 years use (64%), p value = 0.20

Table 3

Adjuvant Hormone Therapy Use for Hormone Receptor Positive Postmenopausal Women with Early Stage Breast Cancer

In Women's Health Initiative Cohort[1]	Kaiser Permanente Southern California[2]	In SEER Population by Survey[3]	Kaiser Permanente Northern California[4]
3,588 surveyed 2009–2010	22,850 in years 1996–2006	743 surveyed in years 2005–2007	13,753 studied in year 1996–2007
Use AI 33%, SERM 31%, mix 36%	Use: SERM 38%, 19% AI, mix 16%	Use: Endocrine 75%	Not examined
17% none	24% none	10.8% none	30% none
33% of users became non-adherent	21% users became non-adherent	15.1% uses became non-adherent by year 4	Not examined

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Table 4

Correlates Associated with Discontinuing Endocrine Therapy or Non-Adherence

Reason	Study
Side effects	Demissie 2001, Kahn 2007, Lash 2006, Cluze 2012
Higher co-morbidity	Hershman 2010, Hadji 2013, Sedjo 2011
Financial considerations or low SES	Kimmeck 2001, Neugut 2011, Liu 2013, Riley 2011
Very young or older age	Hershman 2010, Owusu 2008, Land 2011
Lack of physician recommendation	Davidson 2007
Perception of low risk of recurrence	Fink 2004
Lack of social support	Cluze 2013, Land 2011
Follow-up care with general practitioner vs. oncologist	Murphy 2012
African American race/ethnicity	Hershman 2010
Cigarette smoking	Land 2011
Presence of anxiety/depression linked to better adherence	KyverNitankis 2013, Hadji 2013
Alcohol use	Land 2011