Patient Compliance with Drug Regimen and Global Treatment Efficacy

Breast Cancer

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Rowan T. Chlebowski MD, PhD
Professor of Medicine
David Geffen School of Medicine at UCLA

Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center
Compliance with breast cancer oral medication regimens is a recognized clinical issue and concern

Present status

More questions than answers
Definitions: Adherence vs Persistence

Adherence: the extent to which patients take therapy as prescribed

Persistence: continuing therapy for the prescribed duration (discontinuation rate)

Related but different: A patient can be persistent but non-adherent, but cannot be adherent but non-persistent.
Adherence in Chronic Disease Varies by Drug Class

12-Month Adherence by Drug Class Using Prescription Claims Data\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Proportion of Days Covered (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral contraceptives</td>
<td>54.8</td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td>56.5</td>
</tr>
<tr>
<td>Angiotensin-receptor blockers</td>
<td>60.7</td>
</tr>
<tr>
<td>Statins</td>
<td>62.1</td>
</tr>
<tr>
<td>Statins</td>
<td>64.9</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>83</td>
</tr>
<tr>
<td>Endocrine therapy for breast cancer</td>
<td></td>
</tr>
</tbody>
</table>

ACE=angiotensin-converting enzyme.

Patient Component – Reasons for Not Taking Medications

- Forgot to take: 64%
- Had no symptoms or they went away: 36%
- Wanted to save money: 35%
- Considered drug ineffective: 33%
- No longer needed the therapy: 31%
- Side effects were painful or frightening: 28%
- Drug prevented other activities: 25%
- Had no Rx reminder: 20%
- Problem getting Rx filled: 20%

N=1648

Adherence and Persistence Higher in Clinical Trials Compared to Clinical Practice
Discontinuation Rates in Select Placebo-Controlled Tamoxifen Clinical Trials

IBIS-I=International Breast Cancer Intervention Study.


*Median follow-up in months.*
# Review of Studies Reporting Prevalence of Adherence and/or Persistence to Adjuvant Hormone Therapy in Clinical Practice Settings

<table>
<thead>
<tr>
<th>Information Source</th>
<th>Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescription and Medical Claims Database/Registry</td>
<td>15</td>
</tr>
<tr>
<td>Medical Record Review of Hospital Database</td>
<td>8</td>
</tr>
<tr>
<td>Patient Self-Report</td>
<td>6</td>
</tr>
<tr>
<td>Prospective Studies</td>
<td>4</td>
</tr>
</tbody>
</table>
Review
Adherence and Persistence to Adjuvant Breast Cancer Hormonal Therapy in Clinical Practice

• Prevalence of adherence
  – In tamoxifen users (41% to 88%)
  – In aromatase inhibitor users (50% to 91%)

• Prevalence of therapy discontinuation (Persistence)
  – In tamoxifen users (15% to 20% in first year to 31% to 60% at end of year 5)
  – In aromatase inhibitor users (5% to 25% in the first 2 years)
Prescription Claims Study of Tamoxifen Adherence in Clinical Practice

- Retrospective analysis of prescription claims database (1990-1996) evaluating rates of days covered by *filled prescriptions*

**Long-Term Adherence to Adjuvant Tamoxifen (1991 Cohort)**

<table>
<thead>
<tr>
<th>Year</th>
<th>Overall Adherence, % (mean)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>83</td>
<td>492</td>
</tr>
<tr>
<td>2</td>
<td>68</td>
<td>329</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>309</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>309</td>
</tr>
</tbody>
</table>

Adjuvant Anastrozole Adherence in Clinical Practice

- 3-year retrospective analysis of claims from 3 prescription claims databases of >12,000 women with breast cancer receiving adjuvant anastrozole
- Adherence defined by a Medication Possession Ratio (MPR)
  - MPR = proportion of days covered/observation period (12-month minimum)
  - For a subset of patients, a full 3-year observation period was available and 3-year adherence rates are shown
  - Patients with MPRs <80% were classified as “nonadherent”

Proportion of Adherent and Non-adherent Patients Taking Adjuvant Anastrozole

~1 in 4 women with early breast cancer may be suboptimally adherent to adjuvant ARIMIDEX therapy during the first year of treatment.

Database A
(n=158; n=118; n=94)

Database B
(n=360; n=239; n=191)

Database C
(n=481; n=336; n=251)

Year 1
Year 2
Year 3

Nonadherent  Adherent

Note: decline in sample size due to metastatic disease or death.
Use of Tamoxifen and Aromatase Inhibitors in the UK General Practice Database (1998-2008)

Adherence/persistence less in younger woman. Adherence/persistence greater in AI vs tamoxifen users.

Huiart et al. Br J Cancer 2011;104:1558-1563
Aromatase Inhibitor Crossover Trial and Discontinuation for Musculoskeletal Symptoms

Younger age and prior taxane more likely to discontinue AI therapy

Huiart et al. Br J Cancer 2011;104:1558-1563
Letrozole vs Exemestane Adjuvant: Time to Discontinuation for Musculoskeletal Symptoms

Less discontinuation with letrozole for musculoskeletal symptoms
Exemestane for Breast-Cancer Prevention in Postmenopausal Women

Paul E. Goss, M.D., Ph.D., James N. Ingle, M.D., José E. Alés-Martínez, M.D., Angela M. Cheung, M.D., Ph.D., Rowan T. Chlebowski, M.D., Ph.D., Jean Wactawski-Wende, Ph.D., Anne McTiernan, M.D., John Robbins, M.D., Karen C. Johnson, M.D., M.P.H., Lisa W. Martin, M.D., Eric Winquist, M.D., Gloria E. Sarto, M.D., Judy E. Garber, M.D., Carol J. Fabian, M.D., Pascal Pujol, M.D., Elizabeth Maunsell, Ph.D., Patricia Farmer, M.D., Karen A. Gelmon, M.D., Dongsheng Tu, Ph.D., and Harriet Richardson, Ph.D., for the NCIC CTG MAP.3 Study Investigators*
## MAP.3 Serious Adverse Effects by Severity and Treatment Arm

<table>
<thead>
<tr>
<th>Serious toxicities</th>
<th>Exemestane n(%)</th>
<th>Placebo n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>106 (4.7%)</td>
<td>111 (49%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Clinical skeletal fractures</td>
<td>149 (6.7%)</td>
<td>143 (6.4%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>37 (1.7%)</td>
<td>30 (1.3%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Other malignancies</td>
<td>43 (1.9%)</td>
<td>38 (1.7%)</td>
<td>0.58</td>
</tr>
<tr>
<td>Therapy stopped for toxicity</td>
<td>351 (15.4%)</td>
<td>242 (10.8%)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Placebo Adherence, Clinical Outcomes, and Mortality in the Women’s Health Initiative Randomized Hormone Therapy Trials

Associations between adherence to placebo and risk of fracture, coronary heart disease, cancer, and all-cause mortality where examined in 13,444 postmenopausal women in the WHI trials evaluating estrogen plus progestin or estrogen alone

<table>
<thead>
<tr>
<th>Placebo Adherence</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50%</td>
<td>926</td>
</tr>
<tr>
<td>50-80%</td>
<td>2153</td>
</tr>
<tr>
<td>≥ 80%</td>
<td>10,365</td>
</tr>
</tbody>
</table>

Adjusted Variables in the WHI Analyses of Association Between Placebo Adherence and Clinical Outcomes

- Adjusted for age, ethnicity, education, smoking, alcohol, fruit/vegetables intake, red meat intake, BMI, physical activity, physical function, any insurance, mammogram, care provider visit history, colonoscopy ever, family history of fracture or breast cancer, self-reported health, history of diabetes, bilateral oophorectomy, age at first birth, age at menarche, depression, aspirin, corticosteroids, fracture medication, beta blockers, thiazides, loop diuretics, PPIs, NSAIDs, lifetime hormone therapy duration, medication number
Relation Between Placebo Adherence ($< 80\%$ vs $> 80\%$) and Clinical Events in the WHI Menopausal Hormone Therapy Trials

<table>
<thead>
<tr>
<th>Event</th>
<th>Events</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (all cause)</td>
<td>464</td>
<td>0.64 (0.51-0.80)</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>127</td>
<td>0.50 (0.33-0.78)</td>
</tr>
<tr>
<td>Clinical MI</td>
<td>241</td>
<td>0.69 (0.50-0.95)</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>265</td>
<td>0.73 (0.53-1.00)</td>
</tr>
<tr>
<td>Cancer death</td>
<td>215</td>
<td>0.60 (0.43-0.82)</td>
</tr>
</tbody>
</table>

Women who adhered to placebo use had substantially more favorable clinical outcomes compared to non-adherence which was not explained by potential confounders.
Does Adherence/Persistence with Hormone Therapy Influence Breast Cancer Outcomes?
Early Breast Trialist Cooperative Group: Tamoxifen for Early Breast Cancer

30,000 cases with ER positive or unknown tumors and about 10 years follow-up

<table>
<thead>
<tr>
<th>Trial Duration</th>
<th>Proportional Recurrence Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>21% (SD 3)</td>
</tr>
<tr>
<td>2 years</td>
<td>29% (SD 2)</td>
</tr>
<tr>
<td>5 years</td>
<td>47% (SD 3)</td>
</tr>
</tbody>
</table>

P trend < 0.00001

EBCTCG Cochrane Database Syst Rev 2001;(1):CD000486
Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial

Prof Garnet L Anderson PhD, Prof Rowan T Chlebowski MD, Aaron K Aragaki MS, Prof Lewis H Kuller MD, Prof JoAnn E Manson MD, Prof Margery Gass MD, Elizabeth Bluhm MD, Prof Stephanie Connelly MD, Prof F Allan Hubbell MD, Prof Dorothy Lane MD, Lisa Martin MD, Prof Judith Ockene PhD, Prof Thomas Rohan MBBS, Prof Robert Schenken MD, Prof Jean Wactawski-Wende PhD
Estrogen Alone Influence on Breast Cancer Incidence: Intent-to-Treat vs Sensitivity Analysis

Factors Influencing Non-Adherence in Breast Cancer Prevention Trials

Additional prescription medication \(^1\) and not smoking \(^1, 2\) predicted better adherence

Alcohol \(^2\) use and side effects were negative predictors

\(^2\) Land et al. J Clin Oncol 2010;28:15s
Predictors of Non-Adherence to Aromatase Inhibitors

- Medication possession ratio (MPR) for 1 year of AI therapy in Colorado (USA) breast cancer patients with early stage disease
- 23% of 13,593 were non-adherent (< 80% MPR)
- Associated with non-adherence, younger age, patient cost ≥ 30 $ per prescription

Cost
Endocrine Therapy Among Hormone Receptor-Positive Breast Cancer Patients Enrolled in Medicare Part D Who Reached Coverage Gap

Non-adherence increased for those without low income subsidy for AIs

Riley et al. Medicare and Medicaid 2011;1(4):E1-E26
Hypothesis: adherence highest when anxiety regarding disease is highest

Study of 28 patients on adjuvant hormonal therapy showed:

- Oncologists and patients had good rapport and open communication
- *However, the issue of adherence was poorly addressed*
- Persistence was addressed (12 of 28 visits), but mostly in the context of planned time on therapy
- Discussions of hormonal therapy
  - Focused on medication inventory, side effects, and study/trial findings
- Oncology nurses in these offices were not observed interacting with patients regarding oral therapy (possibly due to practice structure)
# Adjuvant Hormone Therapy for Receptor Plus Postmenopausal Women with Early Stage Breast Cancer

<table>
<thead>
<tr>
<th>Link SEER Medicare Part D Data</th>
<th>In Women’s Health Initiative Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>15,542 in years 2003-2005</td>
<td>3,588 surveyed 2009-2010</td>
</tr>
<tr>
<td>Use: SERM 22%, AI 52%</td>
<td>Use: AA 33%, SERM 31%, mix 36%</td>
</tr>
<tr>
<td>26% none</td>
<td>17% none</td>
</tr>
<tr>
<td>20-30% of users became non-adherent</td>
<td>33% of users became non-adherent</td>
</tr>
<tr>
<td>Lack of physician recommendation (12%) most common barrier</td>
<td></td>
</tr>
</tbody>
</table>


Toman, LaCroix, Chlebowski (submitted)
Physician Component
Prescription Refill, Patient Self-Report and Physician Report
and Adherence to Hormone Therapy in Early Breast Cancer
A Retrospective Cohort Study

<table>
<thead>
<tr>
<th>Odds Ratio Associated with Adherence for Each of the Methods Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician Report</td>
</tr>
<tr>
<td>N(%)</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>Age at diagnosis</td>
</tr>
<tr>
<td>5-74</td>
</tr>
<tr>
<td>≥75</td>
</tr>
<tr>
<td>P-value</td>
</tr>
</tbody>
</table>

Physicians overestimate adherence

Font, et al. British J Cancer 2012;1-8
Adherence and Persistence with Oral Adjuvant Capecitabine in Older Women in CALGB 49907

Adherence among participants by cycle using the microelectronic monitoring system (MEMS) indicates relatively good adherence to oral chemotherapy.

Signs and Predictors of Poor Adherence and Persistence

- Missed appointments, inadequate follow-up
- Poor patient-provide relationship
- Unfilled prescriptions
- Adverse effects from medication, mediation cost
- Lack of belief in treatment
- Psychological problems, particularly depression

Model of Adherence and Persistence

**Personal Factors**
- Emotional state
- Health beliefs
- Social supports
- Feelings about disease, self-efficacy & outcome expectations
- Socioeconomic status

**Treatment Factors**
- Reason for therapy
- Schedule
- Immediacy & evidence of benefit
- Side effects
- Costs

**Interaction With System**
- Relationship with providers
  - Satisfaction with care
  - Insurance coverage
  - Convenience of clinics

**Adherence & Persistence**
Interventions for Improving Adherence

• Increased accessibility to healthcare
  – More convenient follow-up appointments
  – Access to pharmacists, behavioral specialists, social workers

• Improved dosing plan

• Educational intervention to increase patient’s understanding of:
  – Disease characteristics
  – Risks and benefits of treatment
  – Proper use of medication

• While these are general recommendations, they reflect clinical trial approach

Only modest information about factors associated with continued adjuvant hormonal therapy are known.

Few of the correlates identified are easily modifiable

Current medical claim databases, commonly used, contain limited information on healthcare practice patterns or patient characteristics needed to identify modifiable factors

Few proposed remedies have clinical trial efficacy support