A Review of the Literature Evaluating Adherence and Persistence to Adjuvant Endocrine Therapy

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Mini Review

The use of adjuvant endocrine therapy (ET, e.g. tamoxifen or aromatase inhibitors: anastrozole, letrozole, exemestine) for five to ten years is the standard of care for individuals with hormone receptor positive breast cancer [1]. ET has resulted in impressive reductions in disease recurrence and mortality [2]. When taken as prescribed, these agents can reduce recurrence by 30-50% and reduce mortality by approximately one third irrespective of treatment with chemotherapy [2,3]. As evidence of the survival advantage of ET has mounted, taking the drug daily as directed (adherence) and continuing treatment as prescribed for 5-10 years (persistence) have emerged as potential contributors to differences in therapeutic effect. Adherence to the correct daily dose of ET becomes more problematic over the expected five or more years of treatment, ranging from 79.6% after year 1 to 68.3% after year 5. Persistence across the 5-year period is also problematic ranging from 13.6% in year 1 to 40.9% in year 5 [4].

Adherence is defined as the degree of conformity to provider prescription with regard to timing, dosage, and frequency of day-to-day medication use. It has been operationalized in adjuvant breast clinical trials as having possession of a supply of medication to cover 80% or more days over a given time period [5]. In a systematic review of 29 adjuvant ET adherence studies, Murphy showed that adherence to ET in clinical practice settings ranged from 41-72%. Adherence was slightly higher among those receiving aromatase inhibitors (50-91%) versus tamoxifen (41-88%). This was somewhat lower than previous retrospective analyses of clinical trials data in which adherence was higher, 50-90%, raising the concern that adherence rates observed in clinical trials may not represent a real-life setting.

The reasons for non-adherence or non-persistence of ET are not entirely clear, but there is evidence that side effects such as hot flashes, joint aches and stiffness may contribute a great deal [5-7]. In the Mammary Prevention [3] (MAP3) breast cancer prevention trial, it was noted that patients with negative changes in the menopausal specific quality of life questionnaire had early rates of treatment discontinuation [8]. Additionally, it demonstrated that non adherent breast cancer survivors expressed more difficulty managing side effects and perceived fewer benefits when side effects were bothersome [9]. Persistence refers to the duration from initiation to discontinuation of therapy. It has been operationalized variously as no more than 45, 90, or 180 days elapsed without prescription renewal. A retrospective evaluation of prescription fills showed that the median duration of tamoxifen therapy was 2.42 years with 51% discontinuing before 5 years.

In a large review by Murphy et al., it was noted that extremes of age (i.e. younger or older), increasing out-of-pocket costs, follow up care with general practitioner (vs. oncologist), and side effects were all mainly negatively associated with adherence [10-25]. On the flip side, it was found that taking more medications at baseline, referral to an oncologist, and earlier age at diagnosis were mostly associated with adherence or persistence [10,11,14,19,26-28]. Furthermore, patients that switched from tamoxifen to an aromatase inhibitor after 2-3 years were less likely to be adherent [10,11,26].

Only a few interventions to improve adherence have been evaluated in the setting of adjuvant ET. There is evidence in the clinical trial setting of higher adherence and duration of therapy, suggesting that increased contact from health care providers could be of benefit [29]. Research has shown that educational materials and reminders did not increase adherence to ET [29-31]. Two randomized trials that compared educational materials about ET with standard care showed no difference in adherence after 1 year [29,32]. Another intervention trial with a small sample compared standard care versus mailings (5 letters year 1 and 3 letters year 2) versus telephone calls (5 calls year 1; 3 calls year 2) to improve adherence to aromatase inhibitors [31].

Although the three intervention groups did not differ, a pooled analysis comparing both interventions with standard care showed that frequent contact was superior to standard care.
Another study evaluated the use of standard of care to standard of care plus a patient support group. Results of this study showed 1-year persistence rates of nearly 96% in both groups, but no difference between the two arms [33]. No intervention studies focused on management of ET-related symptoms as a means of improving adherence to therapy. Given that side effects may contribute to discontinuation or issues with adherence, methods to improve upon the most common side effects can be implemented [5-7]. For example, both serotonin and norepinephrine reuptake inhibitors (SNRIs, e.g. venlafaxine) and selective serotonin reuptake inhibitors (SSRIs, e.g. fluoxetine) have been shown to decrease the amount of vasomotor symptoms such as hot flashes that patients experience [34,35].

For arthralgia complaints, there is a lack of effective treatment options, but patients may find benefit from non-steroidal anti-inflammatory drugs (NSAIDs), exercise, and/or weight loss [36]. Interestingly, the only intervention for which there is prospective, randomized data to support its use in aromatase inhibitor associated arthralgia is acupuncture [37]. Vaginal dryness and sexual dysfunction are common complaints [38]. For dryness, water based lubricants are usually recommended [36]. Even though topical estrogens are occasionally recommended in severe cases, there is concern for systemic absorption which could lead to an increased risk of breast cancer recurrence. Although data from large randomized trials is lacking, studies of small patient cohorts suggest that the use of topical estrogens may not increase the risk of recurrence [39].

The American College of Obstetricians and Gynecologists recommend that among women with a history of estrogen-dependent breast cancer who are experiencing urogenital symptoms, vaginal estrogen should be reserved for those patients who are unresponsive to non-hormonal remedies [40]. They conclude that treatment should be individualized based on each woman’s risk–benefit ratio and clinical presentation. Currently, there is no standard approach to ensure that patients remain adherent to ET. Ongoing studies continue to evaluate various methods in which to address barriers to oral therapy adherence. It is likely that a personalized approach may be needed as the reasons in which patients tend to be non-adherence are not universal amongst all patients taking adjuvant endocrine therapy. Furthermore, clinical trials have shown that physician reporting of symptoms is neither sensitive nor specific, but that patient reported outcome measures have increased levels of sensitivity and can improve quality of life and overall survival in certain settings [41,42]. Therefore, it may also be of benefit to use patient-reported outcomes to closely monitor ET related adverse symptoms. As practitioners, we must continuously evaluating patient adherence to oral therapy and address any barriers to adherence and persistence such as side effects, costs and patient understanding of the importance of maintaining adequate adherence to such therapies. In particular, close attention to modifiable risk factors for non-adherence and non-persistence such as side effects is of the upmost importance.

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