Prevalence and Determinants of Adherence to Oral Adjuvant Endocrine Therapy among Breast Cancer Patients in Singapore

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ABSTRACT

Objective: The success of oral adjuvant endocrine therapy (OAET) is greatly influenced by patients’ level of adherence to treatment. The objective of this study is to measure the prevalence and determinants of adherence to OAET among breast cancer patients in Singapore.

Methods: A cross-sectional survey of patients supplemented by analysis of their prescription records was used to collect data. Adherence to OAET was assessed using the Morisky Medication Adherence Scale-4 items and evaluation of refill gaps. Univariate and multivariate analyses were done to evaluate the association between patients’ characteristics and adherence to OAET.

Results: A total of 157 women who have started OAET at least 6 months before the time of interview participated in the study, of which less than half (64 patients, 40.8%) of the patients had high adherence. Univariate analysis identified patients who were 57 years or older (P = 0.027), unemployed (P = 0.027), on aromatase inhibitors (P = 0.023), on three or more concurrent medications (P = 0.001), and had one or more comorbidities (P = 0.000) to be significantly more adherent. However, only the number of comorbidities was found to be an independent predictor of adherence in a multiple logistic regression analysis (adjusted odds ratio = 2.60; 95% confidence interval = 1.208–5.593; P = 0.015). Forgetfulness was the main reason for nonadherence mentioned by 63 (67.7%) of the 93 nonadherent patients.

Conclusions: Low level of OAET adherence was found in this study, and forgetfulness was cited as the main reason for nonadherence. Patients were generally receptive to the implementation of various strategies to assist them with their medication-taking behavior.

Key words: Adherence, breast cancer, hormonal therapy, oral adjuvant endocrine therapy

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**Introduction**

Oral adjuvant endocrine therapy (OAET) is recommended to reduce the risk of recurrence and mortality in women who received primary treatment for estrogen or progesterone receptor positive breast cancer.\(^1\) OAET involves the use of agents such as tamoxifen or the third-generation aromatase inhibitors (letrozole, anastrozole, and exemestane).\(^2\) It has long been established that the use of OAET is associated with improvements in disease-free survival in hormone receptor-positive breast cancer patients.\(^3,4\) The success of therapy depends on how patients are taking their medications for the duration of therapy. However, studies show that poor adherence to OAET is a significant clinical problem.\(^5\)

Nonadherence to OAET could potentially lead to dire clinical and economic consequences.\(^6,7\) An obvious consequence of a reduction in dose-intensity due to nonadherence is the loss of treatment efficacy leading to increased risk of recurrence and mortality.\(^7,8\) Moreover, poor adherence is associated with increased costs as a result of disease complications, the need to use additional clinical interventions, and death.\(^9,10\)

Different factors are reported to be associated with low level of adherence to OAET. These include switching of hormonal therapy, extremes of age, increasing out-of-pocket costs, treatment side effects, low recurrence risk perception, suboptimal patient-physician communication, and lack of social support.\(^11-13\) Identifying the factors that influence adherence to OAET is important for the implementation of effective interventions.\(^14\) While there are a number of studies on the prevalence and determinants of adherence to OAET in other parts of the world, there is a paucity of data in Asia, and Singapore is not an exception.

Breast cancer is the leading cause of cancer-related morbidity and mortality among women in Singapore.\(^15\) The country also has one of the highest incidences of breast cancer in Asia.\(^16\) Given the significance of the condition and the need to maintain quality of patient care, there is no doubt about the importance of ensuring adherence to breast cancer treatment. The objective of this study was to quantify the level and determinants of adherence to OAET among breast cancer patients in Singapore and to identify the reasons for nonadherence. Patients’ preferences for different adherence-enhancing strategies were also assessed.

**Methods**

**Study design and participants**

A cross-sectional survey in combination with a retrospective analysis of patient medical and dispensing records was conducted at a tertiary cancer center in Singapore. Patients had to be female, above 21 years old, residing in Singapore, diagnosed with breast cancer, receiving OAET for at least 6 months, and be able to provide written informed consent. Besides, patients had to be able to speak and understand English or Mandarin. Patients who did not fulfill the inclusion criteria and those with prescriptions from external or private oncologists were excluded from the study. Ethical approval was obtained from the Institutional Review Board, and all participants provided their written informed consent before participation in the study.

**Data collection**

Data collection was done from December 2013 to January 2014, using face-to-face interview with a semi-structured questionnaire and review of medical records using a structured checklist. The questionnaire was prepared based on review of literature and had five sections, namely, (a) demographics, (b) therapy-related information, (c) medication adherence, (d) reasons for nonadherence, and (e) preferred strategies to help improve medication adherence. The questions on respondents’ reasons for nonadherence and their suggested strategies for enhancing adherence were designed as open-ended questions. A list of prompts on the reasons for nonadherence and strategies to improve adherence were prepared to facilitate the interview process. Interviewers employed the list of prompts after obtaining patients’ responses on the open-ended questions. For the structured sections of the questionnaire, interviewers were trained to follow a set of written instructions with exact phrasing of questions to minimize interviewer bias.

**Primary outcome variable**

The primary outcome variable in this study was the level of adherence to OAET. The four-item Morisky Medication Adherence Scale-4 (MMAS-4) originally validated in patients with hypertension was used to determine adherence as it was validated in the broadest range of diseases.\(^17,18\) The four items in the MMAS-4 were designed as yes or no questions. For each item, a “yes” response was scored as 0 and a “no” was scored as 1.\(^19\) In this study, patients with a total score of 4 were deemed to have high adherence while scores of 3 points and ≤ 2 points, respectively, indicated moderate and low levels of adherence. To verify patients’ reported level of adherence, their dispensing records were analyzed for the presence of refill gaps during the entire treatment phase from the start to the most recent tamoxifen or aromatase inhibitor received. A refill gap was defined as having a prescription refilled after the expected refill date based on previous medication supply. Medication switching
and possible surplus from previous fills were taken into account in the calculation. Accordingly, patients with refill gap were considered nonadherent.

**Statistical analysis**

Statistical analysis was performed using IBM SPSS Statistics for Macintosh, Version 23.0. (IBM Corp., Armonk, NY, USA). Statistical tests of association were done by comparing patients who had moderate or low level of adherence, as measured by MMAS-4, with those who had high adherence. The independent variables were also transformed into binary variables for the analysis. Respondents’ answers to the open-ended questions were analyzed based on the preset list of prompts. Responses that were different from this list were coded and analyzed as unique categories of preferred adherence-enhancing strategies and reasons for nonadherence. Univariate analysis (Pearson Chi-square and Fisher’s exact test) was performed to evaluate the effect of sociodemographic and disease- and therapy-related variables on adherence. Factors found to be statistically significant in the univariate analysis were included in the multivariate logistic regression model. \( P \leq 0.05 \) was considered statistically significant.

**Results**

Face-to-face interviews and medical record reviews were conducted for a total of 157 patients. The average age of participants was 56.3 (standard deviation \( \pm 10.4 \)) years. The majority of the participants were Chinese (135, 86.0%), married (116, 73.9%), and under a copayment or a third party payer scheme to cover expenses of their OAET drugs (116, 73.9%) [Table 1]. A total of 104 (66.2%) patients had prior chemotherapy, and slightly more than half (81, 51.6%) were currently on aromatase inhibitors. Moreover, 79 patients (50.3%) had one or more comorbidities, and 77 (49%) were concomitantly taking 3 or more medications [Table 2].

The median MMAS-4 score was 3.0 (interquartile range = 2.0). The proportions of patients with high, moderate and low levels of adherence to OAET were 64 (40.8%), 49 (31.2%) and 44 (28.0%) respectively. Record reviews also showed that 58 (36.9%) patients had no refill gap in the review period. The sociodemographic [Table 1] and clinical characteristics [Table 2] associated with high adherence to OAET were older age (57 years and older) \( (P = 0.027) \), unemployment/being retired \( (P = 0.027) \), being on aromatase inhibitors \( (P = 0.023) \), having one or more comorbidities \( (P < 0.001) \), and being on three or more concurrent medications \( (P = 0.001) \). All the five variables that showed significant association with high adherence to OAET were entered into a multivariate logistic regression model. After adjustment for potential confounders, the only variable that was found to significantly predict high adherence to OAET was the presence of one or more comorbidities (adjusted odds ratio \( [OR] = 2.60 \), 95% confidence interval \( [CI] = 1.208–5.593 \)) [Table 3].

Patients who reported moderate or low level of adherence (93 patients, 59.2%) were asked for their reasons for nonadherence. Accordingly, forgetfulness was the reason given by 63 (67.7%) of patients followed by the long duration of therapy (18, 19.4%) and trying to avoid side effects (14, 15.1%) [Table 4]. Although all patients were asked about the strategies that they think will help in improving adherence, only 136 (86.6%) provided specific responses. From these, 83 (61.0%) suggested using pillboxes to organize daily doses as a strategy to improve adherence. Moreover, 74 (54.4%) patients suggested getting education on benefits of their medications and 70 (51.5%) suggested getting education on the nature of their illness as possible strategies to improve adherence [Table 5].

| Table 1: Univariate analysis of the association between the sociodemographic characteristics of respondents and their adherence to oral adjuvant endocrine therapy \( (n = 157) \) |
|---------------------------------|----------|---------------------|----------|
| **Sociodemographic characteristics** | **n (%)** | **Prevalence of high adherence (%)** | **P** |
| **Ethnic background** | | | |
| Chinese | 135 (86.0) | 40.0 | 0.646 |
| Others\(^1\) | 22 (14.0) | 45.5 | |
| **Age, years** | | | |
| 65 and younger | 78 (49.7) | 32.1 | 0.027 |
| 57 and older | 79 (50.3) | 49.4 | |
| **Marital status** | | | |
| Married | 116 (73.9) | 41.4 | 0.792 |
| Single, divorced, or widowed | 41 (26.1) | 39.0 | |
| **Number of children** | | | |
| 1 or more children | 116 (73.9) | 41.4 | 0.792 |
| None | 41 (26.1) | 39.0 | |
| **Living arrangements** | | | |
| Alone | 13 (8.3) | 15.4 | 0.075 |
| With family or someone else | 144 (91.7) | 43.1 | |
| **Highest education level** | | | |
| None, primary | 49 (31.2) | 42.9 | 0.853 |
| Secondary school | 68 (43.3) | 38.2 | |
| Polytechnic, university and above | 40 (25.5) | 42.5 | |
| **Employment status** | | | |
| Employed | 78 (49.7) | 32.1 | 0.027 |
| Unemployed/retired | 79 (50.3) | 49.4 | |
| **Type of payment** | | | |
| Copay or third party pay | 116 (73.9) | 44.8 | 0.081 |
| Fully self-pay | 41 (26.1) | 29.3 | |

*Patients who scored 4 on MMAS-4 were considered to have high adherence. \( P \) value based on Chi-square test. Others refers to Malay, Indians, and others. MMAS-4: Morisky Medication Adherence Scale-4 items. Use of the “MMAS™” is protected by US and International copyright and trademark laws. Permission for use is required. A license agreement is available from: Donald E. Morisky, MMAS Research LLC 14725 NE 20th St. Bellevue WA 98007.
This study documented the level of breast cancer patients’ adherence to OAET from an Asian tertiary care cancer center. As such, the findings will help narrow the research gap on the issue of patient adherence to OAET and its determinants among Asian patients. The study also identified the underlying reasons for nonadherence and potential strategies to promote adherence to OAET.

The overall proportion of breast cancer patients who had high adherence to OAET was found to be less than half (40.8%). Although the adherence rate in this study was lower than most other studies, results were comparable with that reported by Atkins and Fallowfield.\textsuperscript{[20,21]} The variations in the rate of adherence reported by different studies can be attributed to the differences in the study design, study population, and the method of measurement of adherence used.\textsuperscript{[21]} In this study, level of adherence from self-reported subjective data (MMAS-4) was confirmed with the analysis of prescription refill gaps, a fairly objective approach.\textsuperscript{[22]} Adherence rates inferred from both methods were comparable. This implies that patient reports of their adherence levels were reasonably reliable.

There are numerous factors that may influence adherence to OAET, and the literature sometimes shows conflicting reports regarding the direction of influence of some of the factors.\textsuperscript{[23]} The univariate analysis in this study identified five factors as significantly associated to high adherence. These factors were age ($P = 0.027$), employment status ($P = 0.027$) [Table 1], type of OAET taken ($P = 0.023$), number of comorbidities ($P < 0.001$), and number of chronic medications ($P = 0.001$) [Table 2]. However, only the number of comorbidities was found to be an independent predictor of high adherence in a multiple logistic regression analysis (adjusted OR $= 2.60$; 95% CI $= 1.208–5.593$; $P = 0.015$). The absence of statistical significance with the other variables can partly be explained by the small sample size of the study.

Univariate analysis showed that women who were 57 years and older were significantly more likely to have high adherence to OAET ($P = 0.024$). This is consistent with the different studies that have shown association of nonadherence with younger age.\textsuperscript{[5,20]} Moreover, younger age (<45 years) and age $\geq$85 years were reported to be reliable predictors of nonadherence to adjuvant tamoxifen therapy.\textsuperscript{[23]} Participants of our study were relatively younger, with age range from 25 years to 84 years. Hence, the assumption that women older than 85 years tend to be nonadherent might not apply to our study population. Besides, we found that patients who had one or more comorbid conditions and were taking three or more medications were more likely to have high adherence to their OAET. Other studies also reported similar findings, especially for the positive effect of taking more number of medications on adherence to OAET.\textsuperscript{[24,25]}

### Table 2: Univariate analysis of the association between the clinical- and medication-related characteristics of respondents and their adherence to oral adjuvant endocrine therapy ($n = 157$)

| Characteristics                                      | $n$ (%) | Prevalence of high adherence (%) | $P$   |
|------------------------------------------------------|---------|---------------------------------|-------|
| **Type of OAET taken for the past 1 month**           |         |                                 |       |
| Tamoxifen                                            | 76 (48.4) | 31.6                            | 0.023 |
| Aromatase inhibitors                                  | 81 (51.6) | 49.4                            |       |
| **Side effects**                                     |         |                                 |       |
| No side effects reported                              | 75 (47.8) | 45.3                            | 0.265 |
| One or more side effects                              | 82 (52.2) | 36.6                            |       |
| **Cancer stage at diagnosis**                         |         |                                 |       |
| Stage 0                                               | 10 (6.4)  | 50.0                            | 0.293 |
| Stage 1                                               | 46 (29.3) | 32.6                            |       |
| Stage 2                                               | 69 (43.9) | 39.1                            |       |
| Stage 3                                               | 32 (20.4) | 53.1                            |       |
| **Prior chemotherapy**                                |         |                                 |       |
| No                                                    | 53 (33.8) | 34.0                            | 0.216 |
| Yes                                                   | 104 (66.2) | 44.2                           |       |
| **Years since first OAET**                            |         |                                 |       |
| $\leq$2                                               | 73 (46.5) | 47.9                            | 0.088 |
| $>2$                                                  | 84 (53.5) | 34.5                            |       |
| **Number of comorbidities**                           |         |                                 |       |
| None                                                  | 78 (49.7) | 25.6                            | <0.001|
| $\geq$1                                               | 79 (50.3) | 55.7                            |       |
| **Total number of chronic medications**               |         |                                 |       |
| $\leq$2                                               | 80 (51.0) | 27.5                            | 0.001 |
| $\geq$3                                               | 77 (49.0) | 54.5                            |       |

Patients who scored 4 on MMAS-4 were considered to have high adherence, $P$ value based on Chi-square test. OAET: Oral adjuvant endocrine therapy; MMAS-4: Morisky Medication Adherence Scale-4 Items.

### Table 3: Multiple logistic regression analysis of factors associated with adherence among Singaporean breast cancer patients currently on oral adjuvant endocrine therapy ($n = 157$)

| Sociodemographic and clinical factors | Adjusted OR (95% CI) | $P$   |
|--------------------------------------|----------------------|-------|
| **Age (years)**                      |                      |       |
| 56 and younger                       | 1.00                 | 0.960 |
| 57 and older                         | 1.021 (0.444-2.348)  |       |
| **Employment status**                |                      |       |
| Employed                             | 1.00                 | 0.417 |
| Unemployed/retired                   | 1.359 (0.648-2.849)  |       |
| **Number of comorbidities**          |                      |       |
| None                                 | 1.00                 | 0.015 |
| $\geq$1                              | 2.60 (1.208-5.593)   |       |
| **Total number of chronic medications** |                    |       |
| $\leq$2                              | 1.00                 | 0.241 |
| $\geq$3                              | 1.630 (0.721-3.687)  |       |
| **Type of OAET taken for the past 1 month** |                  |       |
| Tamoxifen                            | 1.00                 | 0.226 |
| Aromatase inhibitors                 | 1.615 (0.743-3.512)  |       |

OR: Odds ratio; CI: Confidence interval; OAET: Oral adjuvant endocrine therapy.

### Discussion

This study documented the level of breast cancer patients’ adherence to OAET from an Asian tertiary care center. As such, the findings will help narrow the research gap on the issue of patient adherence to OAET and its determinants among Asian patients. The study also identified the underlying reasons for nonadherence and potential strategies to promote adherence to OAET.

The overall proportion of breast cancer patients who had high adherence to OAET was found to be less than half (40.8%). Although the adherence rate in this study was lower than most other studies, results were comparable with that reported by Atkins and Fallowfield.\textsuperscript{[20,21]} The variations in the rate of adherence reported by different studies can be attributed to the differences in the study design, study population, and the method of measurement of adherence used.\textsuperscript{[21]} In this study, level of adherence from self-reported subjective data (MMAS-4) was confirmed with the analysis of prescription refill gaps, a fairly objective approach.\textsuperscript{[22]} Adherence rates inferred from both methods were comparable. This implies that patient reports of their adherence levels were reasonably reliable.

There are numerous factors that may influence adherence to OAET, and the literature sometimes shows conflicting reports regarding the direction of influence of some of the factors.\textsuperscript{[23]} The univariate analysis in this study identified five factors as significantly associated to high adherence. These factors were age ($P = 0.027$), employment status ($P = 0.027$) [Table 1], type of OAET taken ($P = 0.023$), number of comorbidities ($P < 0.001$), and number of chronic medications ($P = 0.001$) [Table 2]. However, only the number of comorbidities was found to be an independent predictor of high adherence in a multiple logistic regression analysis (adjusted OR $= 2.60$; 95% CI $= 1.208–5.593$; $P = 0.015$). The absence of statistical significance with the other variables can partly be explained by the small sample size of the study.

Univariate analysis showed that women who were 57 years and older were significantly more likely to have high adherence to OAET ($P = 0.024$). This is consistent with the different studies that have shown association of nonadherence with younger age.\textsuperscript{[5,20]} Moreover, younger age (<45 years) and age $\geq$85 years were reported to be reliable predictors of nonadherence to adjuvant tamoxifen therapy.\textsuperscript{[23]} Participants of our study were relatively younger, with age range from 25 years to 84 years. Hence, the assumption that women older than 85 years tend to be nonadherent might not apply to our study population. Besides, we found that patients who had one or more comorbid conditions and were taking three or more medications were more likely to have high adherence to their OAET. Other studies also reported similar findings, especially for the positive effect of taking more number of medications on adherence to OAET.\textsuperscript{[24,25]}
The presence of comorbidities was also reported to be predictive of adherence and persistence to OAET. Women who were unemployed and those currently on aromatase inhibitors were more likely to have high adherence to their medications. The association between employment and nonadherence is rarely examined, and the already available data fail to show association between employment status and adherence. Different studies showed that tamoxifen users were more likely to be nonadherent than those taking aromatase inhibitors, which could be attributable to differences in the side effect profiles of these agents. In this regard, the findings of this study were consistent with the literature although the limited sample size and the absence of significance in the multiple regression analysis may limit the generalizability of the findings.

Patients were asked about their reasons for nonadherence, and 63 (67.7%) of the 93 patients deemed to have moderate or low level of adherence based on MMAS-4, cited forgetfulness. As much as this is a widely reported reason for OAET nonadherence, it should also be seen with caution. This is because it is likely that patients may find it easier and more convenient to report “forgetting” to take their medicines since it is a relatively more socially desirable answer than reporting an intentional action not to take them. The other reasons reported by patients for OAET nonadherence were the long duration of therapy and attempts to avoid potential side effects. However, the proportions of patients citing these reasons were very low (19.4% and 15.1%, respectively) compared to those who blamed forgetfulness [Table 4].

Promotion of adherence to OAET should include teaching and counseling of patients to enhance their knowledge about the purpose and expected outcomes of medication treatment and their skills for self-management of side effects. Monitoring the adherence behavior of patients and provision of feedback are also important. In line with this, patients in this study suggested a variety of strategies that they believed could be useful to improve their adherence to OAET. While the use of pillboxes to organize daily doses was the most widely suggested strategy, the rest of highly recommended strategies focused either on educational interventions to increase patients’ awareness on their illness and the benefits and side effects of their medications or the use of face-to-face or telephone-based monitoring of their medication-taking patterns [Table 5].

**Limitations**

Although this study has shed light on the level and determinants of OAET adherence among breast cancer patients in Singapore, the findings should be interpreted with limitations in mind. Most importantly, a small convenient sample was used. Hence, most of the factors that were known to influence OAET adherence in other studies were not found to be significant in our study. In addition,
the MMAS-4 has not been validated in patients with breast cancer despite being validated in a broad range of diseases. This might have had an influence on the data quality of this study. In this study, semi-structured interviews were used with the objective of obtaining the maximum amount of information about patients’ reasons for nonadherence and their preferred strategies to improve adherence. In line with this, patients who preferred to talk in Mandarin were allowed to share their views despite using a semi-structured questionnaire prepared in English. About 40% of interviews were done this way, and this might have introduced some level of bias in the results of the study.

Conclusion

This study documented suboptimal OAET adherence rate of 40.8% among breast cancer patients. Sociodemographic factors such as older age and being unemployed/retired and clinical- and medication-related factors such as having one or more comorbidities, being on aromatase inhibitors and being on three or more chronic medications were associated with high adherence in a univariate analysis. However, the presence of one or more comorbidities was identified as the only independent predictor of high adherence in a multivariate logistic regression analysis. The most widely cited reason for nonadherence was forgetfulness followed by the long duration of therapy and trying to avoid medication side effects. As patient education is at the heart of most interventions to enhance patient adherence, strategies developed should be targeted to increase patient medication knowledge and their skills for self-management. Different modes of delivery should also be considered, and future research should focus on establishing the effectiveness of such interventions in breast cancer patients.

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Conflicts of interest

There are no conflicts of interest.

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