

Cognitive functioning during long-term tamoxifen treatment in postmenopausal women with breast cancer

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Abstract

Objective: Endocrine therapy is widely used—often for many years—in women with breast cancer. Yet little is known about cognitive functioning after long-term use of tamoxifen. We examine cognitive sequelae, approximately 3 years after diagnosis, in postmenopausal women with breast cancer who were treated with adjuvant tamoxifen.

Methods: Data from participants who underwent surgical operation with or without radiotherapy, participants who received adjuvant tamoxifen, and healthy controls were collected. Neuropsychological tests were administered, and participants completed questionnaires on health-related quality of life (Quality of Life Questionnaire Core 30 and Breast Cancer–Specific Quality-of-Life Questionnaire), menopausal symptoms (Functional Assessment of Cancer Therapy—Breast endocrine symptom subscale), and anxiety and depression (Hopkins Symptom Checklist).

Results: In total, 107 women participated (adjuvant tamoxifen group, $n = 20$; surgical operation/radiotherapy group, $n = 43$; healthy control group, $n = 44$). Women in the adjuvant tamoxifen group had received tamoxifen for a mean (SD) of 31.5 (18.6) months (range, 15–79 mo) and performed worse on verbal memory than the surgical operation/radiotherapy group ($P < 0.05$) and the healthy control group ($P < 0.05$). Participants in the adjuvant tamoxifen group performed worse on measures of fluency than healthy controls ($P < 0.05$). Furthermore, women in the adjuvant tamoxifen group reported worse cognitive functioning ($P < 0.05$) than women in the surgical operation/radiotherapy group or the healthy control group.

Conclusions: Our results provide insights into cognitive functioning in women who receive long-term adjuvant tamoxifen treatment. By adding the surgical operation/radiotherapy group, we could control for the mental and physical influences of the diagnosis and treatment of breast cancer. Cognitive domains that rely on verbal abilities (verbal memory and fluency) seem to be at risk for deterioration after treatment with tamoxifen.

Key Words: Tamoxifen – Cognition – Postmenopausal – Breast cancer.

With increased survival, cognitive functioning after breast cancer therapy becomes of greater importance to the well-being of women. In postmenopausal women, approximately 75% of breast tumors are hormone-sensitive.¹ In this group of women, endocrine therapy is widely used and often prescribed for many years.

Endocrine therapy aims to inhibit the growth of estrogen receptor (ER)-positive tumors by inhibiting or blocking estrogen. This can be achieved by administering either selective ER modulators (SERMs), which allow selective inhibition or stimulation of estrogen-like action in various tissues, or aromatase

inhibitors (AIs), which block the synthesis of estrogen, thus lowering estrogen levels. These endocrine therapies may be provided in a switch schedule (initially SERMs for a number of years followed by an AI up to a total of 5–7 y of endocrine therapy).^{2,3} Common adverse effects of endocrine therapy, such as hot flashes and mood disturbances, are related to estrogen deprivation.⁴ Increasing evidence suggests that estrogens play a role in cognitive functioning.⁵ Although the mechanisms of action of estrogens on the brain are not entirely understood, neuroscientific studies indicate that estrogens exert neurotrophic and neuroprotective actions.⁶ Estrogens seem to favor differentiation and survival by acting through ERs,⁷ but estrogens also act through membrane receptors to influence the functioning of the brain.⁸ These ERs are present in structures that are important for cognitive functioning, such as the frontal lobe and the hippocampus.⁹ Therefore, it is biologically plausible that endocrine therapy could affect cognitive functioning. Moreover, because estrogen is known to interact with the cholinergic system,¹⁰ it seems probable that cognitive functions such as attention, verbal learning, and memory may be particularly vulnerable.

Although much is already known about the cognitive effects of chemotherapy,¹¹ many women with breast cancer receive

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Table of Contents Long Term Tamoxifen Treatment For Breast Cancer

1. Understanding the eBook Long Term Tamoxifen Treatment For Breast Cancer
 - The Rise of Digital Reading Long Term Tamoxifen Treatment For Breast Cancer
 - Advantages of eBooks Over Traditional Books
2. Identifying Long Term Tamoxifen Treatment For Breast Cancer
 - Exploring Different Genres
 - Considering Fiction vs. Non-Fiction
 - Determining Your Reading Goals
3. Choosing the Right eBook Platform
 - Popular eBook Platforms
 - Features to Look for in an Long Term Tamoxifen Treatment For Breast Cancer
 - User-Friendly Interface
4. Exploring eBook Recommendations from Long Term Tamoxifen Treatment For Breast Cancer
 - Personalized Recommendations
 - Long Term Tamoxifen Treatment For Breast Cancer User Reviews and Ratings
 - Long Term Tamoxifen Treatment For Breast Cancer and Bestseller Lists
5. Accessing Long Term Tamoxifen Treatment For Breast Cancer Free and Paid eBooks
 - Long Term Tamoxifen Treatment For Breast Cancer Public Domain eBooks
 - Long Term Tamoxifen Treatment For Breast Cancer eBook Subscription Services

- Long Term Tamoxifen Treatment For Breast Cancer Budget-Friendly Options
- 6. Navigating Long Term Tamoxifen Treatment For Breast Cancer eBook Formats
 - ePub, PDF, MOBI, and More
 - Long Term Tamoxifen Treatment For Breast Cancer Compatibility with Devices
 - Long Term Tamoxifen Treatment For Breast Cancer Enhanced eBook Features
- 7. Enhancing Your Reading Experience
 - Adjustable Fonts and Text Sizes of Long Term Tamoxifen Treatment For Breast Cancer
 - Highlighting and Note-Taking Long Term Tamoxifen Treatment For Breast Cancer
 - Interactive Elements Long Term Tamoxifen Treatment For Breast Cancer
- 8. Staying Engaged with Long Term Tamoxifen Treatment For Breast Cancer
 - Joining Online Reading Communities
 - Participating in Virtual Book Clubs
 - Following Authors and Publishers Long Term Tamoxifen Treatment For Breast Cancer
- 9. Balancing eBooks and Physical Books Long Term Tamoxifen Treatment For Breast Cancer
 - Benefits of a Digital Library
 - Creating a Diverse Reading Collection Long Term Tamoxifen Treatment For Breast Cancer
- 10. Overcoming Reading Challenges
 - Dealing with Digital Eye Strain
 - Minimizing Distractions
 - Managing Screen Time
- 11. Cultivating a Reading Routine Long Term Tamoxifen Treatment For Breast Cancer
 - Setting Reading Goals Long Term Tamoxifen Treatment For Breast Cancer
 - Carving Out Dedicated Reading Time
- 12. Sourcing Reliable Information of Long Term Tamoxifen Treatment For Breast Cancer
 - Fact-Checking eBook Content of Long Term Tamoxifen Treatment For Breast Cancer
 - Distinguishing Credible Sources
- 13. Promoting Lifelong Learning
 - Utilizing eBooks for Skill Development
 - Exploring Educational eBooks
- 14. Embracing eBook Trends

- Integration of Multimedia Elements
- Interactive and Gamified eBooks

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