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Article

Assessing the Effectiveness of Hormonal Aromatase inhibitors (AI) Therapy in Hormone Receptor Positive Post-Menopausal Breast Cancer Patients: A Systematic Review

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ABSTRACT

Background: Endocrine therapy is a cornerstone in the treatment of breast cancer for patients who are hormone receptor-positive (HR+). Aromatase Inhibitors are a key option for managing HR+ breast cancer in postmenopausal women.
Objective: This study investigates the efficacy of Aromatase Inhibitors in postmenopausal women with HR+ breast cancer, focusing on their therapeutic benefits and associated risks.
Methods: A comprehensive literature review was conducted using the Cochrane, Google Scholar, PubMed, Science Direct, ClinicalTrials.gov, and Scopus databases, adhering to PRISMA guidelines. Study quality was evaluated using the Risk of Bias for Randomized Trials (RoB 2.0) tool.
Results: Aromatase Inhibitors function by inhibiting the aromatase enzyme, effectively reducing estrogen production. While they can be used with other therapies such as metformin or saracatinib, these combinations are not significantly more effective. Aromatase Inhibitors have been shown to enhance cognitive function and alleviate some depressive symptoms, although they may increase the risk of depression and anxiety in some patients.
Conclusion: Aromatase Inhibitors are an effective treatment for HR+ breast cancer in postmenopausal women. However, the potential psychological side effects, such as depression and anxiety, require careful management during therapy.

Keywords: Aromatase inhibitors, Breast cancer, Postmenopausal, Estrogen, Progesterone

INTRODUCTION

Cancer is characterized by the growth and spread of abnormal cells within the body. The World Health Organization highlights cancer as a leading cause of death globally. In Indonesia, cervical and breast cancers were the most prevalent in 2013, with breast cancer being the most common type among women. Approximately 80% of breast cancer cases express the Estrogen Receptor (ER) (Gnant et al., 2021; Ningrum & Rahayu, 2021). In the United States, breast cancer remains the most frequently diagnosed cancer, with an estimated 290,560 new cases in 2022 and a mortality rate of around 15%. It is also the second leading cause of cancer-related deaths among women, with approximately 43,250 fatalities (Makkena et al., 2023).

Despite advances in medical technology, a definitive cure for breast cancer has yet to be developed. However, multiple effective treatment options are available to

reduce the risk of mortality. Endocrine therapy, particularly targeting tumors expressing Estrogen and Progesterone Receptors (ER and PR), has become a primary treatment approach due to its effectiveness and minimal side effects. Patients with advanced breast cancer often retain the same hormone receptor profile upon recurrence (Gnant et al., 2021; Aggelis & Johnston, 2019).

One risk factor for breast cancer is late menopause (after age 55), highlighting the need for specialized care in post-menopausal patients. Aromatase Inhibitors represent a cornerstone of endocrine therapy in these patients, especially during the first five years of adjuvant treatment, and are favored over tamoxifen for their greater effectiveness (Mirsyad et al., 2022; Fitzal et al., 2021; García-Sánchez et al., 2022).

Aromatase Inhibitors work by blocking the aromatase enzyme, which converts androgens to estrogen, thus lowering estradiol levels. Their use is not recommended for women with functioning ovaries, as they may stimulate the recovery of ovarian function, potentially reducing the therapy's effectiveness or causing unexpected pregnancies. Determining menopausal status remains a topic of discussion (Krásenská, 2016).

Angela Brodie, a British pharmacologist, pioneered the clinical application of Aromatase Inhibitors in 1982. While various types exist, only Letrozole, Anastrozole, and Exemestane are FDA-approved. Despite their widespread use, debates continue regarding long-term effects, side effects, and patient adherence. Consequently, continued research is needed to enhance the understanding of Aromatase Inhibitors' efficacies and challenges (Makkena et al., 2023).

This study aims to evaluate the effectiveness and side effects of Aromatase Inhibitor therapy in post-menopausal women with hormone receptor-positive breast cancer. By focusing on potential impacts like increased depression and anxiety risk, the study seeks to optimize treatment strategies and improve the quality of life for these patients.

METHODS

Search Strategy

This systematic review was conducted following the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). PRISMA provides a standardized framework for reporting systematic reviews. We sourced literature from several comprehensive databases: Cochrane, PubMed, Google Scholar, Scopus, and ScienceDirect, resulting in an initial pool of 412 journals. These journals were subsequently filtered using predefined inclusion and exclusion criteria.

Data Extraction

Complete reports were assessed to determine if they met the inclusion criteria, encompassing outcomes, interventions, study design, and patient demographics. The reasons for excluding specific studies were documented. Our focus was on post-menopausal women with breast cancer. The study population was divided into two groups: one receiving Aromatase Inhibitors (AI) and the other receiving Aromatase Inhibitors plus a placebo. We monitored the groups for metrics such as objective response rate, clinical benefit, overall survival, and tolerability, with particular attention to differences in the comparison group.

Quality Assessment and Risk of Bias

The quality of the included studies was evaluated using the Risk of Bias 2 (RoB 2) for randomized studies and the Risk of Bias In Non-randomized Studies – of Interventions (ROBINS-I) methods. Cochrane's established tools were utilized to assess factors such as randomization, blinding, statistical analysis, and the handling of drop-outs. We also examined potential biases in sample selection and data handling. This rigorous evaluation ensured that our findings were supported by valid and reliable scientific evidence, consistent with best practices for systematic reviews.

Eligible criteria

The stringent criteria ensured the relevance and quality of the data. Inclusion criteria focused on advanced breast cancer patients who were post-menopausal, with positive hormone receptor status, discussing issues of depression and anxiety, utilizing either randomized controlled trial (RCT) or non-RCT methods, with known population sizes, and published in English after 2013. Exclusion criteria eliminated studies with pre-menopausal patients, negative hormone receptor status, lack of focus on depression and anxiety, and studies employing review methods or presenting unclear results.

Risk of Bias Assessment and Quality Assessment

In our systematic review, we assessed bias and quality using two established tools: the Risk of Bias 2 (ROB-2) tool for randomized controlled trials (RCTs) and the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool. The ROB-2 tool evaluates key domains such as the randomization process, deviations from intended interventions, handling of missing data, measurement of outcomes, and selection of reported results. These domains help determine the potential biases influencing RCT findings and ensure the reliability of the study outcomes. For non-randomized studies, ROBINS-I examines bias through areas like confounding variables, participant selection, intervention classification, and handling of missing data, among others. By systematically addressing these areas, ROBINS-I helps identify and manage biases that could affect the studies' validity.

RESULTS

General Description of Studies

The PRISMA diagram (Figure 1) illustrates our article selection process. Initially, 412 articles were identified using specific keywords. After title screening adjustments, 356 articles remained. Further abstract screenings narrowed this down to 209 articles, ultimately resulting in 5 articles included in the systematic review. These selected studies, published between 2013 and 2023, focused on evaluating the safety and effectiveness of Aromatase Inhibitors in post-menopausal breast cancer patients. While the studies shared a common theme, variations were noted in intervention delivery, session number and duration, assessed outcomes, and overall impact. All studies consistently targeted post-menopausal breast cancer patients, excluding pre-menopausal individuals. Each study assessed and compared the quality-of-life following drug therapy, as summarized in Table 1. The selection process is detailed in Figure 1.

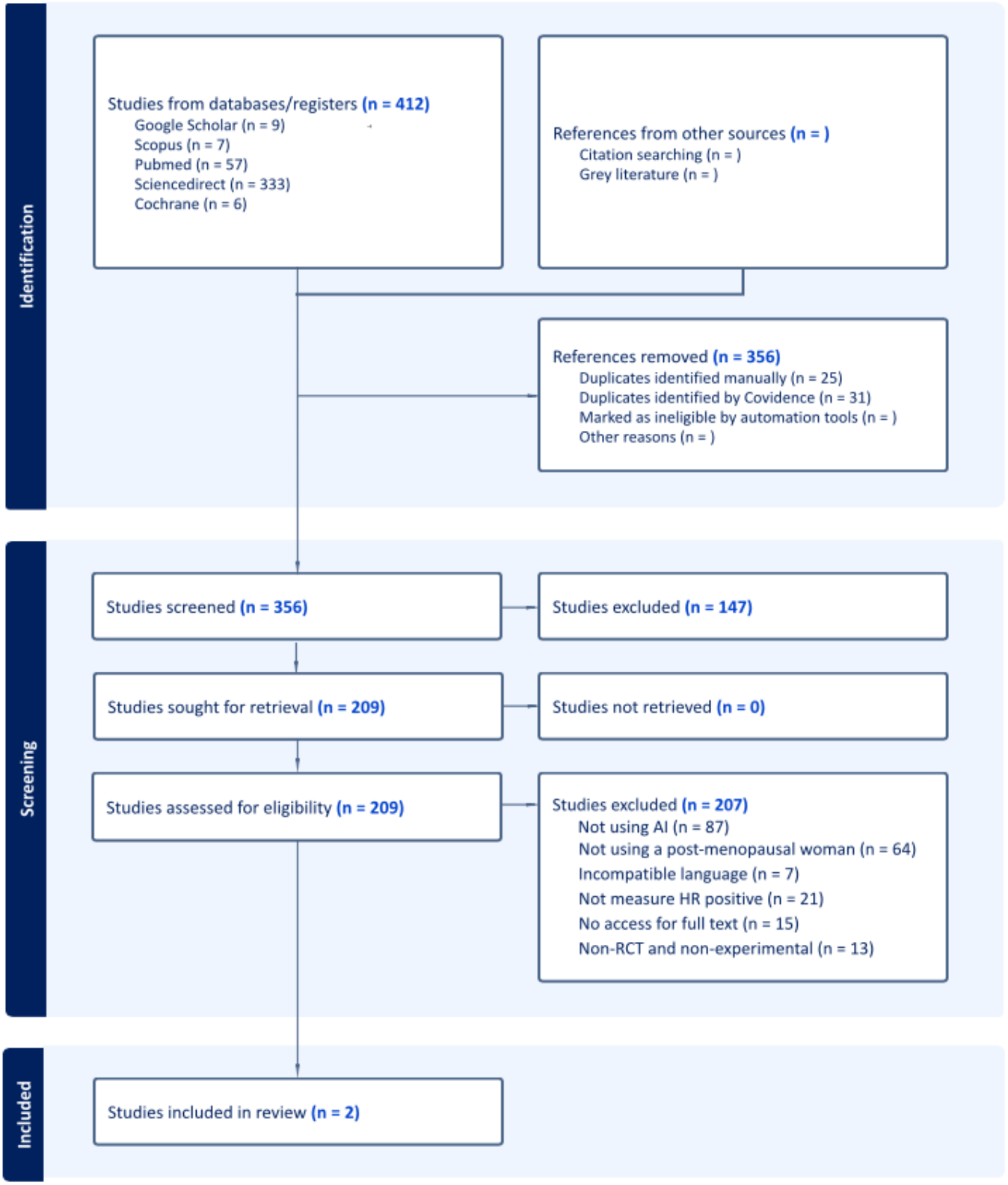

Figure 1. PRISMA Flow diagram

Table 1. Overview of included studies

No.	Title (Year)	Author (Country Where Research was Conducted)	Objective	Population and intervention	Amount	Results and achievements
1	Adjuvant Aromatase inhibitors treatment worsens depressive symptoms and sleep quality in postmenopausal women with localized breast cancer: A one-year follow-up study (2022)	Garcia-Sanchez et al. (Spain)	Evaluating the link between these symptoms and identifying any alterations in the assessments of cognitive performance, depressive symptoms, and sleep quality following a year of AI treatment.	Women with early-stage hormone-dependent breast cancer who had undergone radiation therapy, chemotherapy, and/or tumor removal surgery, as well as those who were about to begin antiestrogen treatment with an AI to prevent recurrence, comprised the study cohort. Cognitive function, depressive symptoms, sleep issues, and the capacity to carry out basic everyday tasks were assessed at baseline, six months, and twelve months after starting adjuvant AI treatment for locally advanced breast cancer in women.	47 participants	After six and twelve months of treatment, there was no discernible decline in cognitive function using Mini-Mental State Examination (MMSE) scores as compared to the baseline. This study's findings—that depression symptoms are rising and sleep quality is declining—have ramifications for medical professionals because they affect patients' quality of life and adherence to therapy.
2	Quality of File and Psychological Functioning in Postmenopausal Women Undergoing Aromatase inhibitors Treatment	Gabriella Martino et al. (Italy)	The aim of this study was to determine the effectiveness of Aromatase inhibitors in reducing symptoms of depression and improving quality of	51 outpatient postmenopausal women with BC made up the study's population, and 51 postmenopausal women in good health made up the control group. The 36-item Short Form Health Survey, the Hamilton Anxiety Rating Scale, the Beck	102 Participants	According to the study's findings, those with breast cancer (n = 51) had lower subjective quality of life and more symptoms of anxiety and depression than those without the disease (n = 51) ($p<0.05$ for all). Following a half-year

No.	Title (Year)	Author (Country Where Research was Conducted)	Objective	Population and intervention	Amount	Results and achievements
	for Early Breast Cancer (2020)		life (QoL) in breast cancer patients.	Depression Inventory II edition, and the clinical gold standard interview were used to assess all recruited participants. The results were compared with controls in BCS during AI treatment at baseline and after six months. All subjects also had their bone mineral density (BMD), vitamin D status, and subclinical vertebral fractures evaluated. Information was gathered on age, menopausal age, body mass index (BMI), alcohol intake, and smoking behaviors.		course of AI treatment, individuals with breast cancer reported notably lower levels of anxiety and depression symptoms as well as a markedly improved physical and mental quality of life when compared to controls.

Study Characteristics and Evaluation Methods

The studies differed in methodology, timing, and follow-up processes during evaluation. Two out of the five studies explored the efficacy of combining Aromatase Inhibitors with other drugs for managing breast cancer. These studies assessed the effects and effectiveness of Aromatase Inhibitors either in combination with other medications or over a specified period using randomized controlled trial designs. Independent reviewers followed a standard data extraction process to evaluate study quality based on predetermined criteria, providing a comprehensive narrative of the main characteristics.

Description of Interventions

Administering Aromatase Inhibitors yielded comparable benefits across all five studies. Notably, an improvement in patients' quality of life was observed, particularly after six months of Aromatase Inhibitor use. One study specifically highlighted the significant reduction in anxiety and depression levels. Of the five studies, two compared Aromatase Inhibitors with other drugs, one explored the optimal duration of use, and two focused on enhancing the quality of life in post-menopausal breast cancer patients.

Effect of Aromatase Inhibitors

The first study indicated that Aromatase Inhibitors impacted depressive symptoms in post-menopausal breast cancer patients (Martino et al., 2020). Breast cancer survivors (n=51) reported higher anxiety and depression symptoms and a lower perceived quality of life than controls (n=51) ($p<0.05$ for all). After six months of AI treatment, survivors experienced significant reductions in anxiety and depression symptoms and improvements in perceived quality of life compared to controls.

The second study highlighted that increased depressive symptoms and decreased sleep quality adversely affected patients' daily lives, potentially impacting adherence to prescribed treatments (Garcia-Sanchez et al., 2022). Poor sleep quality further compromised overall health, increasing susceptibility to other illnesses and healthcare system burdens. This connection between depressive symptoms, sleep quality, and quality of life could extend treatment duration and healthcare costs.

Quality Assessment Analysis

We analyzed 5 journals as the basis for our assessment. By applying the ROB-2 technique to RCT journals and ROBINS-I to non-RCT journals, all were determined to have a low risk of bias. Consequently, the journals selected are of high quality, providing a solid foundation for our systematic review and analysis.

DISCUSSION

This systematic review underscores the pivotal role of third-generation Aromatase Inhibitors (AIs) such as letrozole and anastrozole in treating post-menopausal breast cancer. These AIs achieve notable inhibition rates of up to 99%, demonstrating enhanced efficacy and tolerability over predecessors like megestrol acetate (Makkena et al., 2023; Boszkiewicz et al., 2022). Our findings highlight the substantial improvements in treatment outcomes but also point to the persistent challenges related to the side effects of AI therapy.

AIs have fundamentally transformed breast cancer management in post-menopausal women, showing superior performance to traditional treatments such as estrogen modulators like Tamoxifen and hormonal therapies such as Progestin (Makkena et al., 2023). Letrozole and anastrozole are particularly effective, improving patients' overall survival rates and quality of life. Their usage results in significant reductions in anxiety and depression, particularly after sustained usage

over six months, which amplifies their therapeutic value beyond just survival outcomes (Peters & Tadi, 2023). However, side effects, notably joint pain and decreased bone density, remain critical issues that can impact long-term patient adherence and quality of life. Continued research into these adverse effects is essential for developing interventions that could mitigate these challenges.

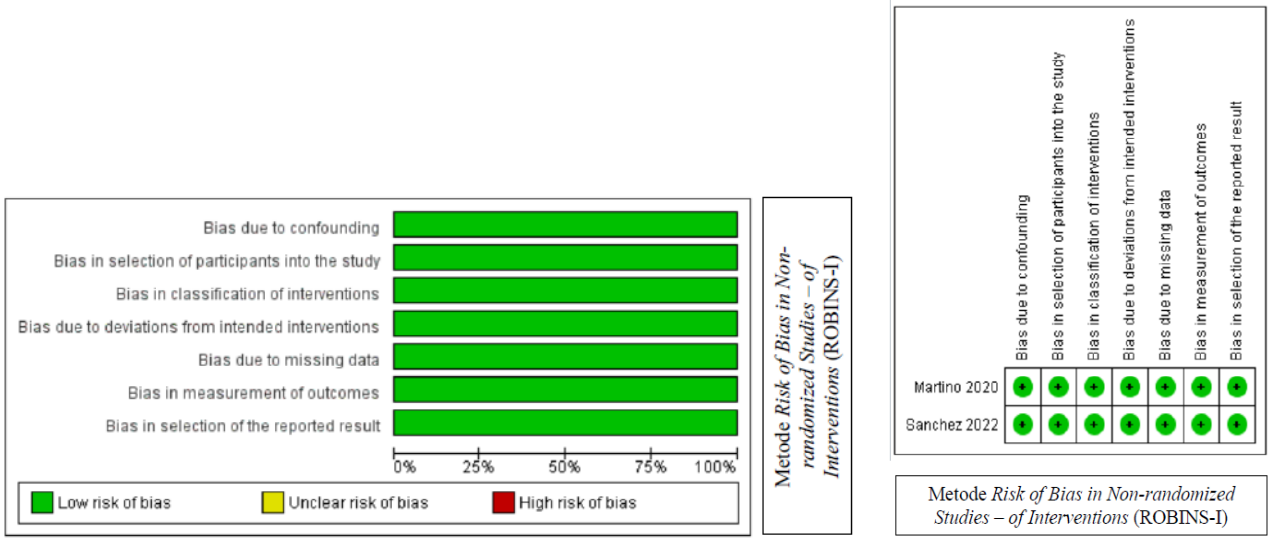

Figure 2. Summary of Quality Assessment of non-RCT Studies using the ROBINS-I

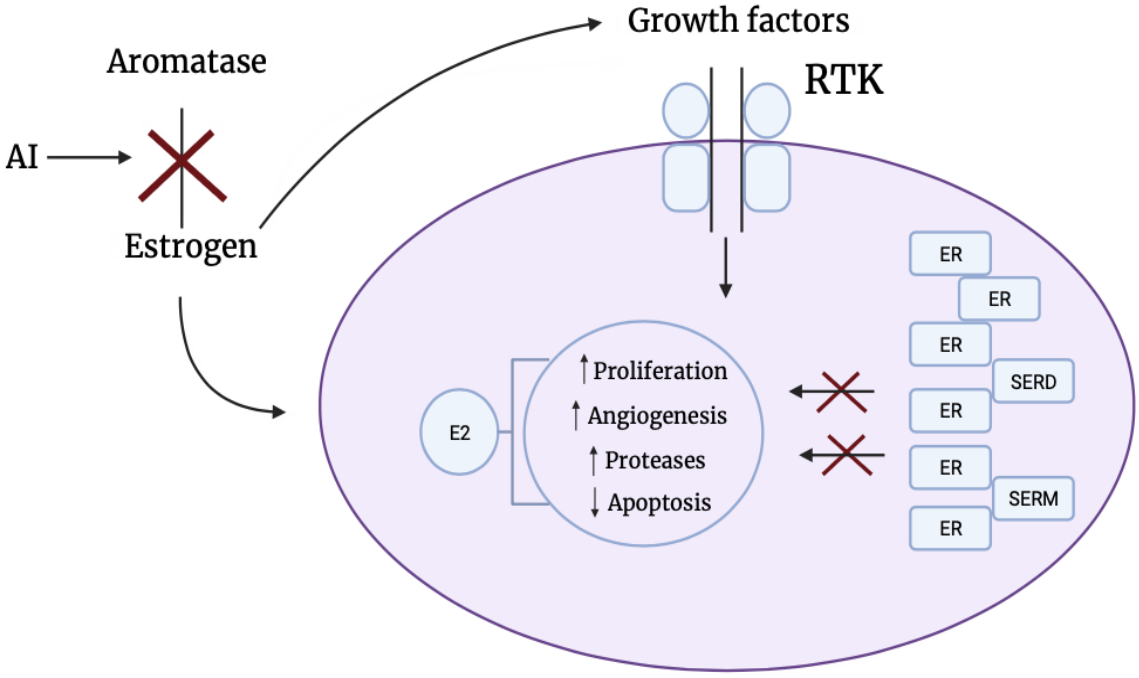

Figure 3. Metabolic pathways of Estrogen Receptor (ER) Positive Cells affected by AI

The psychological effects, particularly concerning depression and anxiety, highlight the need for a holistic approach to cancer care. While these AIs are medically effective, the increase in depressive symptoms during treatment (as reported by García-Sánchez et al., 2022) necessitates integrated mental health support. This ensures not only the physical health of patients but also maintains their mental well-being throughout the treatment process. By incorporating regular psychological assessments and interventions as part of standard cancer care, the overall outcomes of AI therapies could be optimized, leading to better patient adherence and satisfaction.

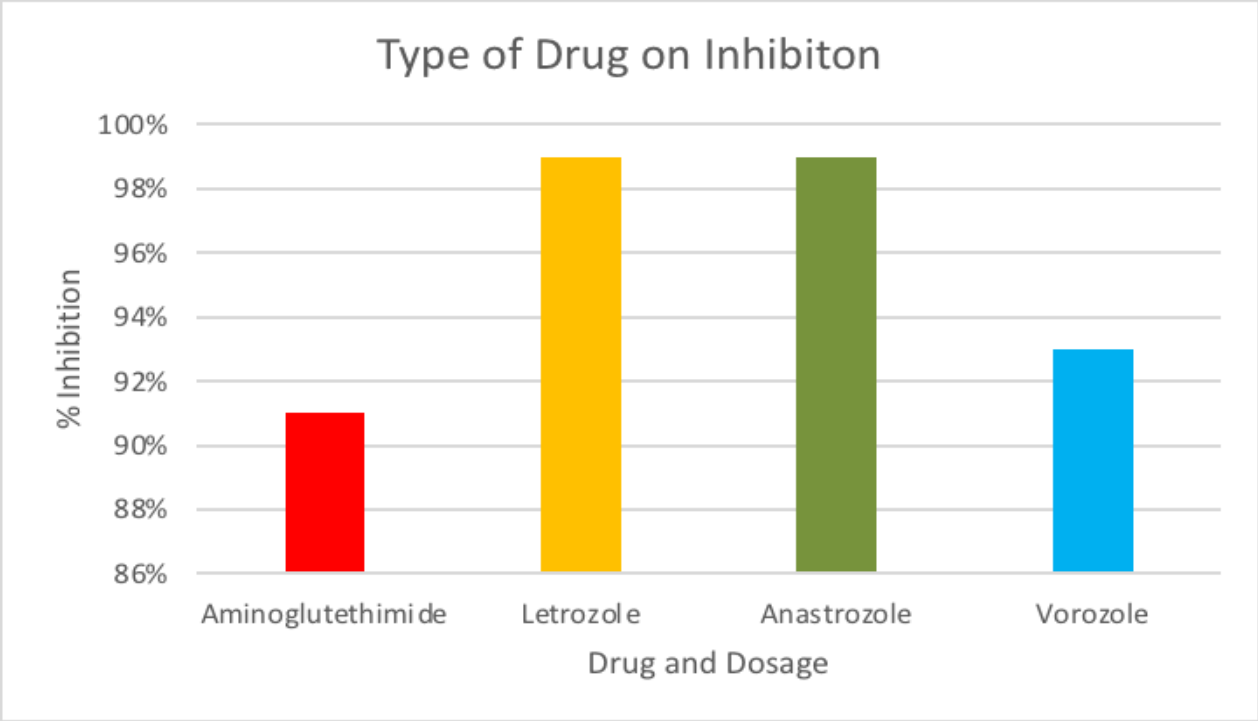

Figure 4. Graph of Aromatase inhibitors of various generations, including their dose levels, and percent inhibition

Moreover, clinical findings suggest that adjunctive therapies, though used alongside AIs, do not significantly enhance efficacy beyond what AIs provide alone. This highlights the importance of prioritizing AI therapies in treatment plans and also points to the need for further research to explore possible synergistic treatment combinations that might offer additional benefits without introducing extra side effects.

From a clinical practice perspective, these findings advocate for the development of comprehensive treatment frameworks. Such frameworks should integrate physical treatment plans with robust psychosocial support strategies. By focusing on holistic care, clinicians can address both the physiological and psychological impacts of breast cancer therapies. Employing regular mental health evaluations and personalized therapeutic interventions can help mitigate the risk of depression and anxiety, enhancing overall treatment adherence and patient outcomes.

CONCLUSION

In conclusion, Aromatase Inhibitors stand as a cornerstone in the treatment of hormone receptor-positive breast cancer among post-menopausal women. While their clinical efficacy is well substantiated, addressing side effects, particularly those impacting psychological well-being, is crucial for maximizing their therapeutic potential. Future research should focus on refining treatment regimens to minimize adverse effects and enhance support systems to manage mental health issues effectively. This integrative approach promises sustainable treatment success and improved quality of life for patients undergoing AI therapy.

CONFLICT OF INTEREST

Author(s) stated that there is no conflict of interest.

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Appendix 1. Study selection
Keyword search in online databases

Cochrane (2013-2023)

No	Search	Results
1	Breast cancer	45,739
2	Post-menopausal	3,937
3	Hormone receptor sensitive	630
4	*Aromatase inhibitors*	1,906
5	Depression and anxiety	10733
6	#1 AND #2 AND #3 AND #4	6
7	#1 AND #2 AND #3 AND #4 AND #5	0

Total: 6

Pubmed (2013-2023)

No	Search	Results
1	Breast cancer	8,788
2	Relapse	19,972
3	Postmenopause	3,109
4	Hormone receptor positive	1,256
5	*Aromatase inhibitors*	557
5	Depression and anxiety	10733
6	#1 AND #2 AND #3 AND #4 AND #5	57
7	#1 AND #2 AND #3 AND #4 AND #5	0

Total: 57

Google Scholar (2013-2023)
("Breast Cancer") AND ("Post-Menopausal") AND ("Hormone Receptor Sensitive") AND ("Aromatase inhibitors") AND (“Depression”) OR (“Anxiety”)
Total: 9

Scopus (2013-2023)
"Breast Cancer" AND "Relapse" AND "Menopause" AND "HR" AND "Aromatase inhibitors" AND “Depression” OR “Anxiety”
Total: 7

Sciencedirect (2013-2023)
Breast cancer, relapse, menopause, hormone receptor positive, Aromatase inhibitors, depression, anxiety
Total: 333