**Supplementary Material**

**Preventive drug therapy and contralateral breast cancer: Summary of the evidence of clinical trials and observational studies**

Annet Bens, Rikke Langballe, Jonine L. Bernstein, Deirdre Cronin-Fenton, Søren Friisand Lene Mellemkjær

Appendix 1. Side effects………………………………………………………… Page 2

References………………………………………………………………………. Page 3

**Appendix 1. Brief summary of possible side effects of the preventive drugs discussed in the review.**

|  |  |
| --- | --- |
| **Drug** | **Possible side effect** |
| **Type** | **Frequency** |
| **Tamoxifen [1, 2]** | Hot flushes and night sweats Vaginal discharge and dryness Low mood Loss of sex drive Irregular menstruation | Common  |
| Endometrial cancer Thromboembolic events Stroke  | Less common or rare  |
| **Aromatase inhibitorsa [3, 4]** | Nausea Fatigue Musculoskeletal complaintsHot flushes and night sweats Vaginal discharge and dryness Low mood Loss of sex drive Bone demineralization (may lead to fractures) | Common  |
| Hypertension Hyperlipidemia Cardiac disordersb | Less common or rare  |
| **Bisphosphonatesc [5]**  | NauseaFatigue Influenza-like symptoms  | Common  |
| Oesophageal reactions Osteonecrosis of the jaw Renal dysfunction Hypocalcemia  | Rare  |
| **Statins [6, 7]** | Myopathy New-onset diabetes Hemorrhagic stroke | Very rare  |
| **Metformin [8]**  | Diarrhea Nausea Abdominal discomfort Lack of energy Headache Metallic taste in the mouth  | Common /rare  |
| **Non-steroidal anti-inflammatory drugs** **[9, 10, 11]** | Nausea or vomitingIrritation of the stomach Gastro-intestinal adverse eventsdPeptic ulcersd Thrombotic cardiovascular events Renal adverse events  | Common  |
| **Anti-hypertensives [12]** | Headache or dizziness Dry mouth Cough Emotional distress or fatigue Cold hands and feet  | Common, but only in mild degree |
| **Fenretinide [13]** | Diminished dark adaptation Dermatological disordersGastrointestinal symptoms Disorders of the ocular surface  | Common, but only in mild degree |

NSAID, non-steroidal anti-inflammatory drug

aMost studies have reported adverse events / side effects for aromatase inhibitors in comparison to tamoxifen.

b The increase in cardiac events observed for AIs compared with tamoxifen is likely due to the cardioprotective effects of tamoxifen.

c Adverse effects vary depending on the type of bisphosphonate prescribed.

d Primarily aspirin and non-selective NSAIDs.

**References**

1. Smith GL. The Long and Short of Tamoxifen Therapy: A Review of the ATLAS Trial. Journal of the advanced practitioner in oncology. 2014 Jan-Feb;5(1):57-60. PubMed PMID: 25032035; eng.

2. Day R, Ganz PA, Costantino JP, et al. Health-related quality of life and tamoxifen in breast cancer prevention: a report from the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Clin Oncol. 1999 Sep;17(9):2659-69. doi: 10.1200/jco.1999.17.9.2659. PubMed PMID: 10561339; eng.

3. van de Velde CJ, Rea D, Seynaeve C, et al. Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial. Lancet. 2011 Jan 22;377(9762):321-31. doi: 10.1016/s0140-6736(10)62312-4. PubMed PMID: 21247627; eng.

4. Garreau JR, DeLaMelena T, Walts D, et al. Side effects of aromatase inhibitors versus tamoxifen: the patients’ perspective. The American Journal of Surgery. 2006 2006/10/01/;192(4):496-498. doi: 10.1016/j.amjsurg.2006.06.018.

5. O'Carrigan B, Wong MHF, Willson ML, et al. Bisphosphonates and other bone agents for breast cancer. Cochrane Database of Systematic Reviews. 2017 (10). doi: 10.1002/14651858.CD003474.pub4. PubMed PMID: CD003474.

6. Svensson E, Nielsen RB, Hasvold P, et al. Statin prescription patterns, adherence, and attainment of cholesterol treatment goals in routine clinical care: a Danish population-based study. Clinical Epidemiology. 2015 02/26;7:213-223. doi: 10.2147/CLEP.S78145. PubMed PMID: PMC4345937.

7. Mach F, Ray KK, Wiklund O, et al. Adverse effects of statin therapy: perception vs. the evidence - focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. Eur Heart J. 2018;39(27):2526-2539. doi: 10.1093/eurheartj/ehy182. PubMed PMID: 29718253; eng.

8. Heckman-Stoddard BM, DeCensi A, Sahasrabuddhe VV, et al. Repurposing metformin for the prevention of cancer and cancer recurrence [journal article]. Diabetologia. 2017 September 01;60(9):1639-1647. doi: 10.1007/s00125-017-4372-6.

9. Cuzick J, Otto F, Baron JA, et al. Aspirin and non-steroidal anti-inflammatory drugs for cancer prevention: an international consensus statement. The Lancet Oncology. 2009 May;10(5):501-7. doi: 10.1016/s1470-2045(09)70035-x. PubMed PMID: 19410194; eng.

10. Gunter BR, Butler KA, Wallace RL, et al. Non-steroidal anti-inflammatory drug-induced cardiovascular adverse events: a meta-analysis. Journal of clinical pharmacy and therapeutics. 2017 Feb;42(1):27-38. doi: 10.1111/jcpt.12484. PubMed PMID: 28019014; eng.

11. Fine M. Quantifying the impact of NSAID-associated adverse events. The American journal of managed care. 2013 Nov;19(14 Suppl):s267-72. PubMed PMID: 24494609; eng.

12. Bardage C, Isacson DG. Self-reported side-effects of antihypertensive drugs: an epidemiological study on prevalence and impact on health-state utility. Blood pressure. 2000;9(6):328-34. PubMed PMID: 11212061; eng.

13. Cazzaniga M, Varricchio C, Montefrancesco C, et al. Fenretinide (4-HPR): a preventive chance for women at genetic and familial risk? Journal of biomedicine & biotechnology. 2012;2012:172897. doi: 10.1155/2012/172897. PubMed PMID: 22500077; PubMed Central PMCID: PMCPMC3303873. eng.