Low dose, continuous combined hormone therapy

Effective relief of menopausal symptoms

Contains drospirenone, a unique progestogen with anti-aldosterone properties

- Significant benefit on elevated blood pressure
- Adds to the blood pressure lowering effects of antihypertensives, i.e. enalapril

References:

S4 ANGELIQ® Film-coated tablets. The pack contains 28 hormonal red film-coated tablets each with estradiol hemihydrate 1.033 mg (equivalent to estradiol 1.0 mg) and drospirenone 2.0 mg. RSA Reg. No.: 37/21.8.2/0451. Namibia Reg. No.: 04/21.8.2/1466. Bayer (Pty) Ltd, Reg. No.: 1968/011162/07, 27 Wrench Road, Sandton, 1609. Tel: +27(0) 11 191 5000. For full prescribing information, please refer to the package insert approved by the Medicines Regulatory Authority. LZA.MKT.WH.01.2016.0954.
Contents

Editorial
Dr SP Moodley

BRCA Gene Mutations - Clinical Conundrums
Dr Anthony B Koller

The management of vasomotor symptoms in patients with a history of breast cancer
Dr Michael Davey

Sexuality in breast cancer survivors
Dr SP Moodley

NOFSA response to the article “Menopause Matters” by Athol Kent. Menopause Focus Vol 4 No 3, Aug 2016, 15-16
Dr Stanley Lipschitz, Dr Tobias De Villiers, Dr Michael Davey

Response to the article “Menopause Matters”, Menopause Focus Vol 4 No3, Aug 2016, 15-16 - Letter to the editor

SAMS News

Editorial Board

Dr Percy Moodley
Editor
Executive Committee Member, SAMS, Ethekweni, Umhlanga and Victoria hospitals
KwaZulu-Natal

Professor Peter Roos
President of SAMS
Adjunct Associate Professor, Department of Gynaecology, UCT, Cape Town

Dr Tobie de Villiers
Past president of the International Menopause Society
Chairman National Osteoporosis Foundation South Africa (NOFSA)
Gynaecologist in Private Practice
Cape Town

Professor Franco Guidozzi
Gynaecologist
Park Lane Clinic
Lecturer, Dept of O&G and Medical School of University of Witwatersrand, Johannesburg

Dr Carol Thomas
Specialist Training and Consultant
Groote Schuur Hospital
Owner and Director, iMobiMaMa, theWomanSpace
Cape Town

Dr Malikah van der Schyff
Obstetrics and Gynaecology
Mediclinic Constantiaberg
Plumstead, Cape Town

The content contained in this publication contains medical or health sciences information and is intended for professional use within the medical field. No suggested test or procedure should be carried out unless, in the reader’s judgement, its risk is justified. Because of rapid advances in the medical sciences, we recommend that the independent verification of diagnoses and drug dosages should be made. Discussions, views, and recommendations as to medical procedures, products, choice of drugs, and drug dosages are the views of the authors. The views expressed by the editor or authors in this newsletter do not necessarily reflect those of the sponsors or publishers. The sponsors, publishers and editor will not be liable for any damages or injuries of any kind arising from the use or misuse of information provided in this publication and do not support the use of products for off label indications.
Menopause Focus, Volume 4 No 4, 2016 coincides with SAMS 2016 congress. I extend best wishes for what promises to be an exciting event.

The aim of Menopause Focus is to educate in the care of women in the climacteric and to enable the practitioner to provide comprehensive care. It provides a unique opportunity for preventive medicine.

The South African Menopause Society (SAMS) is grateful for the educational grant provided by pharmaceutical companies and the fact that they do not interfere with the scientific content of the journal. The society also wishes to encourage scientific debate. In Volume 4, No 3, 2016, we published extracts from Menopause Matters (Bone health) written by Professor Athol Kent. This is available on the SAMS website. NOFSA and Dr Peter de Jong have responded. I welcome correspondence and encourage readers to suggest topics for the future.

Inherited gene mutations have the potential to inhibit the protective effect of apoptosis and DNA repair. Dr Koller provides an insight into the clinical conundrums of BRCA gene mutations. He highlights the public health benefit of prophylactic bilateral salpingectomy for women undergoing benign gynaecological surgery. The importance of assessing hormone receptivity of tumours determines the place of adjuvant tamoxifen. Hormone therapy use does not adversely influence the risk in BRCA 1 and 2 mutation carriers. This evidence provides comfort to sufferers of an acute menopause as a consequence of prophylactic bilateral salpingo-oophorectomy.

Dr Mike Davey gives clarity on the absolute increased incidence of breast cancer in patients using hormonal therapy. The latter rather than relative incidence figures is the information that needs to be imparted to patients during counselling. In symptomatic breast cancer survivors, the present evidence indicates the need for effective non hormonal alternatives. Often the treatments used in breast cancer survivors worsen the symptoms of the climacteric. Individualised selection of patients for the appropriate non hormonal treatment will help improve the quality of life in breast cancer survivors.

Sexual health is a fundamental human right. Age must not be assumed to be a barrier to sexual fulfilment if desired. All health care providers must be able to detect sexual difficulties, especially in patients with chronic health issues. The patient can then be directed for specific help.

Enjoy the congress.
BRCA Gene Mutations - Clinical Conundrums

Dr Anthony B Koller
Gynaecologist/Gynaecological Oncologist
Part-Time Consultant Dept. of O & G, University of Cape Town

The French physician, surgeon, anatomist and anthropologist Pierre Paul Broca is perhaps best known for describing “Broca’s Area” which is situated in the left frontal lobe of the brain in most, (but not all), right-hand-ed people and is responsible for the initiation of speech.

However, this remarkable man had many other interests and achievements, one of which was that in 1866 he extensively studied, and reported, in extraordinary detail, in his book Traité des Tumeurs, on members of a family in in France, whom he noted to be particularly prone to carcinoma of the breast and he astutely considered: - “the possibility of the inheritance of a general diathesis for cancer of the breast in this family.”

It was over a hundred years later in 1972 that Henry T Lynch described the “Lynch Syndromes” also called hereditary nonpolyposis colorectal cancer or (HNPC). These patients, it is now known, have an increased risk of cancers of the stomach, small bowel, liver, gallbladder ducts, upper urinary tract, brain, skin, prostate, endometrium, ovaries and breast.

Since the pioneering work of the above giants in the field of cancer genetics there has been an explosion of research on the clinical implications of BRCA mutations and several important questions arise when clinicians encounter a patient who is a BRCA mutation carrier.

An attempt is made hereunder to find answers to some of these questions from the relevant literature.

Clinical conundrums posed by BRCA mutation carriers

- **What is the profile of a BRCA mutation carrier?**
  People with these mutations account for approximately 5-10% of breast and ovarian cancers and occur with increased frequency in particular populations viz. French-Canadians, Netherlanders, South African Afrikaners, Ashkenazi Jews and Icelanders.

  It is not only the breast and ovary which are at risk in patients who are BRCA mutation carriers they are also at increased risk for cancer of the prostate, male breast, colon, pancreas and melanomas (particularly of the eye). These mutations have also recently been strongly implicated in some haematological malignancies such as acute and chronic myelogenous leukaemia and chronic lymphocytic leukaemia and in many T-cell lymphomas.
• Just how common are breast and ovarian cancer in women with BRCA mutations?

- It is well documented that bilateral mastectomy in patients found to carry the BRCA I or II mutations is associated with an up to 95% protection against the development of breast cancer while bilateral oophorectomy in such patients has a similar 95% protection against the development of ovarian cancer.13,14

With regard to prophylactic oophorectomy it must be mentioned that standard oophorectomy frequently leaves a substantial part of the tube in situ15 (or even the entire tube if the procedure is being performed laparoscopically).

This fact assumes significance when considering recent evidence that a considerable number of serous ovarian carcinomas are thought to originate in the tube and then metastasise to the ovary. Mary B. Daly et al16 have recently opined that: “This evolving appreciation of the role of the fallopian tube in ovarian cancer has led to the consideration of salpingectomy alone as an option for risk management, especially in premenopausal women. In addition, it is postulated that bilateral salpingectomy with ovarian retention (BSOR), may have a public health benefit for women undergoing benign gynaecologic surgery”17.

• What cancer prevention strategies exist for patients with BRCA mutations?

It is well documented that bilateral mastectomy in patients found to carry the BRCA I or II mutations is associated with an up to 95% protection against the development of breast cancer while bilateral oophorectomy in such patients has a similar 95% protection against the development of ovarian cancer.13,14

Whereas level I A evidence exists18 that adjuvant tamoxifen treatment substantially improves the survival of patients with ER positive breast cancer it has been pointed out by Mary-Claire King et al19 that in view of the triple negative nature of BRCA I related tumours, tamoxifen is generally not recommended for prophylaxis in BRCA I mutation carriers while tamoxifen does reduce breast cancer by 62%, in BRCA II mutation carriers (similar to the reduction in incidence of ER-positive breast cancer among all women).

Adjuvant tamoxifen should therefore only be prescribed when appropriate to BRCA1/BRCA2 mutation carriers with hormone receptor positive breast cancer.20

• Does hormone replacement therapy after menopause increase the risk of breast cancer in BRCA1 mutation carriers?

From a 2016 case-control analysis,21 of 432 matched pairs of menopausal women with a BRCA1 mutation, after a mean duration of HRT use of approximately 4.5 years it was calculated that the odds ratio for breast cancer comparing all women who ever used HRT to those who never used HRT was 0.80 (95% CI 0.55-1.16; P = 0.24). These findings suggest that a short course of HRT should not be contra-indicated for BRCA1 mutation carriers who have undergone menopause.

Andrea Eisner et al22 from The Hereditary Breast Cancer Clinical Study Group concurred with this opinion. In the population of BRCA mutation carriers they studied, HRT was also associated with a decreased risk. They go on to state that “We expected this result as most breast cancer in BRCA1 mutation carriers is ER negative”.

• Can HRT be safely prescribed in patients who have undergone breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCAII mutation carriers?

Rebbeck et al23 determined the incidence of breast cancer in 155 women taking HRT who had undergone bilateral prophylactic oophorectomy (BPO) compared to 307 controls. Postoperative follow-up was 3.6 years. HRT of any type after BPO did not significantly alter the reduction in breast cancer risk associated with BPO. (HR 0.37; 95% CI, 0.14 to 0.96) and they concluded that short-term HRT use does not negate the protective effect of BPO on subsequent breast cancer risk in BRCA1/2 mutation carriers.

Risk by age of breast and ovarian cancer in BRCA 1 & 2 mutation carriers


Risk by age of breast and ovarian cancer in BRCA 1 & 2 mutation carriers

Menopause Focus Volume 4 No 4 - November 2016

Menopause Focus Volume 4 No 4 - November 2016

Menopause Focus Volume 4 No 4 - November 2016

Menopause Focus Volume 4 No 4 - November 2016
What of HRT in BRCA mutation ovarian cancer patients?
In a 2004 systematic review of the relevant literature by Hopkins ML et al14 the authors concluded that “HRT is acceptable for patients with ovarian cancer as part of supportive and symptomatic therapy.”

But does this apply to BRCA mutation carriers? Joanne Kotsopoulos et al25 address this question in their study “Hormone replacement therapy and the risk of Ovarian Cancer in BRCA1 and BRCA2 mutation carriers” in which they conducted a case-control study on 162 matched sets of women.

Compared with those who had never used HRT, the odds ratio associated with ever use of HRT was 0.93 (95% CI = 0.56–1.56). There was no significant relationship with increasing duration of HRT use. There was a suggestion that progesterin-based HRT regimens might increase the protection against ovarian cancer (odds ratio = 0.57) but this association was not statistically significant (P = 0.20). They concluded that “HRT use does not appear to adversely influence the risk of ovarian cancer in BRCA mutation carriers”.

Conclusions
A brief review of some of the significant achievements in the fight against hereditary breast and ovarian cancer leading to the discovery of BRCA mutations is sketched. Some of the dilemmas faced by the clinician confronted by a patient who is a BRCA mutation carrier are addressed including: Outlining the profile of a BRCA mutation carrier, the incidence of breast and ovarian cancer in women with BRCA mutations, and the cancer prevention strategies and use of SERM’s and HRT in such patients.

References
9. Schlebusch C M, Dreyer G. Cancer prevalence in 129 breast ovarian cancer families tested for BRCA1 and BRCA 2 mutations SAMJ 2010;100:2:113-117
Breast cancer is the commonest cause of cancer death in women with the incidence of breast cancer reaching a peak between the ages of 50 and 69 years.

Hormone receptor positive breast cancers account for the majority of breast cancers. These tumours have a good prognosis with a high expectation of long-term survival. In these patients, menopause symptoms may occur for a number of reasons:
- Natural menopause concurrent with breast cancer
- Recurrence of symptoms following cessation of hormone therapy
- Risk reducing bilateral oophorectomy
- Chemotherapy
- Ovarian suppression using GnRH agonists
- Endocrine therapy with tamoxifen or aromatase inhibitors

Vasomotor symptoms occur in 85% of breast cancer survivors and are reported as moderate to severe in 63% of these patients. The symptoms are more severe in younger patients and are more severe in women with treatment induced menopause.

The most effective treatment of hot flushes in postmenopausal women who have not had breast cancer is the use of menopausal hormone therapy (HT).

Menopausal hormone therapy and breast cancer

Observational and prospective placebo controlled studies have shown that users of HT have an increased risk of being diagnosed with breast cancer. This risk is related to duration of use and appears to be mainly, but not exclusively, associated with oestrogen plus progestin use. Pivotal studies that have influenced perceptions regarding the link between HT and breast cancer include the Collaborative Group on Hormonal Factors in Breast Cancer, the Million Women’s Study, the Women’s Health Initiative study and the Nurse’s Health Study.

The publication from the Collaborative Group on Hormonal Factors in Breast Cancer provided useful data as to the absolute risk of breast cancer as related to duration of use. Given the expected incidence of breast cancer in North America and Europe between the ages of 50 and 70 years as 45 per 1000 users, it was estimated, based on data from 51 epidemiological studies including 52,705 women with breast cancer and 108,411 women without breast cancer, that the increased incidence after 5 years, 10 years and 15 years of HT use would be 2, 6 and 12 extra cases respectively. (see Table 1)

The Million Women Study reported that the increased risk of breast cancer being diagnosed after 10 years of HT use was 5 per 1000 users for oestrogen only use and 19 per 1000 users for oestrogen plus progestin use.

The Women’s Health Initiative study reported a 26% (RR 1.26 95% CI 1.0-1.09) increased risk of breast cancer when the study was terminated after 5.2 years. In the oestrogen only arm there was no increased risk of breast cancer with up to 7.1 years use with the relative risk being 0.80 (95% CI 0.62- 1.04) in the intention to treat population and 0.67 (95% CI 0.47-0.97) in adherent patients. The Nurses Health Study showed that an increased risk with oestrogen only use was first seen at 15 years with the relative risk after 15 years being 1.42 (95% CI 1.13- 1.77).

Two prospective placebo controlled studies looked at the use of HT in women with breast cancer. The HABITS study was terminated after 2.1 years when data collected showed a doubling of the risk in those women using HT. A sister study, the Stockholm study showed no increased risk of breast cancer but the combined results showed a significantly increased risk and therefore both studies were terminated.

An increased risk of breast cancer recurrence was also found with the use of tibolone in the LIBERATE study.

Although the significance of these figures as regards overall health can be debated, the consequence of this association has been the non-prescription of HT for women with breast cancer. Given the severity and long duration of the symptoms experienced the need for effective non-hormonal alternatives has resulted in numerous drugs being investigated.

---

Table 1: Cumulative risk of breast cancer between the ages of 50 and 70 years (Collaborative Group on Hormonal Factors in Breast Cancer)

<table>
<thead>
<tr>
<th>Duration of Use</th>
<th>Risk of Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never users of HT</td>
<td>45:1000</td>
</tr>
<tr>
<td>5 years use</td>
<td>47:1000</td>
</tr>
<tr>
<td>10 years use</td>
<td>51:1000</td>
</tr>
<tr>
<td>15 years use</td>
<td>57:1000</td>
</tr>
</tbody>
</table>
Non hormonal agents for the treatment of vasomotor symptoms.

Agents with proven efficacy in reducing hot flush frequency include the alpha adrenergic agonist clonidine, selective serotonin and selective nor-adrenaline re-uptake inhibitors, and the gamma-aminobutyric analogues gabapentin and pregabalin.

Clonidine

Clonidine is centrally acting alpha adrenergic agonist with vaso-active properties registered for the treatment of migraine headaches. It is one of the original non-hormonal agents used to treat hot flushes and earlier studies showed it to decrease hot flush frequency by about 46%. In a study comparing 0.075 mg clonidine twice daily to 37.5mg venlafaxine twice daily for the treatment of hot flushes in patients with breast cancer, venlafaxine (see below) was shown to be superior to clonidine in reducing hot flush frequency.12

Selective serotonin re-uptake inhibitors (SSRI’s) and selective nor-adrenaline re-uptake inhibitors (SNRI’s)

Fluoxetine, paroxetine, citalopram and escitalopram have been extensively investigated in this regard. The most widely used agent has been paroxetine and the use of 12.5 mg of paroxetine daily has been shown to decrease hot flush frequency by between 33% and 67%.13

In a meta-analysis of 11 randomised controlled trials comparing the efficacy of SSRI’s, escitalopram was shown to be superior to other SSRI’s in reducing hot flush frequency.14 SSRI’s, however, inhibit CYP2D6, a cytochrome P450 enzyme which converts tamoxifen into active metabolites. This potentially limits the efficacy of tamoxifen and one cohort study has shown increased breast cancer mortality in patients on tamoxifen if treated with paroxetine.15 Escitalopram inhibits CYP2D6 to a lesser extent than the other SSRI’s and the International Menopause Society has recommended that in patients on tamoxifen, either escitalopram or the SNRI, venlafaxine, be used in preference to paroxetine or fluoxetine.16

The SNRI’s have also been shown to be effective in decreasing vasomotor symptoms. A placebo controlled study showed that venlafaxine was superior to placebo but not as effective as estradiol in controlling hot flushes.17 Desvenlafaxine 100mg daily has been compared to placebo in two 12 week studies.

In one of the studies the effect was not superior to placebo but the time to 50% reduction in the number of moderate or severe hot flushes was significantly shorter that seen with placebo.18 In the second study desvenlafaxine was significantly superior to placebo (62% reduction with desvenlafaxine vs 38% with placebo).

Side effects of SNRI’s include nausea, dry mouth, constipation, diarrhoea, fatigue and somnolence.

Gabapentin and pregabalin.

Gabapentin and pregabalin are gamma-aminobutyric acid analogues. Gabapentin has been shown to be effective in decreasing hot flushes. Using doses titrated up to 2400 mg daily resulted in a 71% reduction in flushes.20

A study using 300mg 3 times daily achieved a 51% reduction in hot flush frequency compared to a 26% reduction with placebo. Side effects at the end of week 1 included drowsiness (12%), dizziness (18%) and unsteadiness (14%). These had returned to baseline levels by week 4.21

A study in patients with breast cancer showed a significant reduction of hot flushes with a dose of 300mg 3 times daily but not in a dose of 100mg 3 times daily.22 In view of side effects a commonly used regimen is to start treatment with 300 mg nocte and increase in 300 mg increments at 2 weekly intervals to 900 mg nocte and, if needed, 300 mg in the morning. Gabapentin does not appear to decrease libido, a common side effect seen with SSRI’s.

Pregabalin was shown to be superior to placebo in doses of 75mg twice daily and 150 mg twice daily. Side effects were present in both arms but were fewer in the low-dose arm and in both arms the majority of patients were satisfied with the benefit of hot flush reduction.23

Conclusion

Vasomotor symptoms are amongst the most distressing symptoms affecting women in the menopause transition and the post-menopause and appear to be more severe in women with breast cancer. Practitioners are often frustrated by the perceived lack of effective options for the treatment of hot flushes in these patients. Numerous effective agents are however available. The correct choice of agent will depend on the individual circumstances of each patient.

In a patient with concomitant symptoms of depression or a past history of depression the use of an agent such as venlafaxine or desvenlafaxine would be an obvious choice whereas if sleep disturbances are an issue gabapentin or pregabalin may well be an option. If the patient develops persistent distressing side effects on a particular drug she should be reassured that alternative effective remedies are available.
Although this article has focussed on the medical treatment of vasomotor symptoms, the complexity of the issues facing a woman with breast cancer and indeed her family should be appreciated. Stress is a major factor involved in the causation of hot flushes and stress relief, be it in the form of counselling or encouragement to partake in stress reducing activities such as exercise or yoga should not be overlooked. Weight loss has also been shown to be effective in reducing vasomotor symptoms and correct diet, including simple measures such as avoidance of caffeine containing beverages and alcohol, should be encouraged.

The practitioner who is approached for help by a woman with breast cancer who is experiencing distressing symptoms should, with a detailed individual assessment and a knowledge of the available therapeutic options, be able to offer a meaningful improvement to her quality of life.

References

Sexuality in breast cancer survivors

Dr SP Moodley
Executive Committee Member, SAMS, Ethekweni, Umhlanga and Victoria hospitals, KwaZulu-Natal

Breast cancer survivors constitute the largest group of cancer survivors in the United States. This is a reflection of advances in earlier detection techniques and improvements in surgical and oncological management.¹

Survivorship begins at the time a cancer is detected. It must address health care issues beyond diagnosis and treatment. The quality of life of survivors can be improved by guiding them to the care available, and acknowledging the late effects of treatment. It is estimated that at least 50% of cancer survivors will experience long term sexual dysfunction.²

The predictors of sexual morbidity include:²

- Poor emotional well-being
- Presence or absence of vaginal dryness
- Quality of the relationship
- Partner sexual dysfunction

We must always be cognisant that the treatments offered can have the greatest influence on sexual consequences.

Psychological impact

The younger the patient at the time of diagnosis, the greater the impact. This is due to the features of premature ovarian insufficiency. They have greater concerns about decreased physical activity, weight gain, hair loss and the decline in mental health. There are enormous body image problems. The loss of fertility can be a significant concern for some individuals.

It is important to dissect the effect on the partner. Prediagnosis discord may get exaggerated. Exhaustion due to care giving and not seeing the person with cancer as a sexual partner may warrant counselling.

Chemotherapy

The greatest impact here is also from the symptoms of ovarian insufficiency. The cytotoxic effects of the alkylating chemotherapeutic agents are responsible for the ovarian failure.³ The latter is influenced by the duration and cumulative dose of therapy.

The symptoms include fatigue, nausea, weight fluctuations, alopecia, neuropathy and infertility.

Surgery

There can be varying effects, with once again the impact being greater in younger women. There is a lowered perceived sexual attractiveness.

Breasts are often viewed as a basic part of beauty and womanhood. The touching of breasts is a common part of foreplay; and surgery may interfere with pleasure from breast caressing.

Radiation

There are acute skin changes. The skin can become swollen, red and tender. Nausea, vomiting and fatigue can ensue.

Adjuvant endocrine therapies

Aromatase inhibitors block the conversion of testosterone to estrogen. This leads to severe vulvo-vaginal atrophy. The data on tamoxifen is conflicting. Tamoxifen in fact increases vaginal lubrication by improving atrophy in post menopausal women while it might aggravate atrophy in pre menopausal women.

The most common culprit in causing sexual dysfunction may not be the loss of a breast, but the premature and severe menopausal impact of systemic therapy.

The main concerns in sexual rehabilitation of cancer survivors is that sexuality is poorly addressed in a busy oncology setting. There is poor training of medical professionals, as dysfunctional sexuality is a rare topic in medical curricula. The cancer survivors may minimise sexual issues as they feel shame in desiring intimacy after a life threatening illness.

Sexual rehabilitation should focus on the attainment of a new norm. The important facets in sexual health rehabilitation in cancer patients include:

- Maximising the remaining physiological capacities
- Adaptation to residual limitations by exposing the patient to specialised therapies
- Persistence of rehabilitation efforts in order to ensure a positive outlook for both patient and her partner

Co morbid illnesses often take a back seat in the presence of a diagnosis of cancer. In the rehabilitation process, this needs to be analysed in detail. Medications
that are negatively affecting the sexual response need to be either changed, dose altered or discontinued after discussion with the relevant physician.

The management programme obviously involves guidance to a proper nutrition programme, a healthy exercise regimen and minimal alcohol intake. Addressing time management and privacy concerns must be part of the counselling.

Specific sexual therapy involves assigning sexual tasks or homework which can involve erotic reading assignments, self stimulation exercises, relaxation techniques and use of sensate focus. This aims to build trust and intimacy within a relationship, helping to give and receive. We aim to move the partner from physical intimacy (enjoying each other’s company) to emotional intimacy (sharing desires), then move up a gear to a sensual level where there is erotic content, and finally genital play and penetrative sex, if possible.

The education of a patient or couple may involve the following:

• Teaching of pelvic anatomy, often with the use of hand held mirrors (consider the use of a chaperone if necessary)
• Discussion of the sexual response cycle
• Dispelling of sexual myths
• Improvement of self esteem
• Alternate forms of sexual positioning
• Information on other forms of sexual expression, eg. massaging and caressing
• Effective pain management, often with the aid of genito-pelvic therapists.

In caring for the terminally ill, the attending medical team must ensure privacy for the couple to maintain intimacy if so desired. Sexual connection may provide an opportunity for the cancer patient to say goodbye and also help in closure for the surviving partner.

Hormone therapy

Estrogens and androgens are essential sexual steroids for desire and arousal. Prior to prescribing hormone therapy, the benefit risk profile has to be assessed and proper informed consent taken, especially if off label therapy is used. An individualised evidence based medicine approach is needed.

The first approach in the treatment of vasomotor symptoms in this select group of patients has to be behavioural and environmental modifications plus non-hormonal therapies. Limited knowledge on the aetiology and mechanisms of hot flushing represents a major obstacle for the development of new targeted, non hormonal treatments and no current alternatives are as effective as estrogen.

Clonidine, selective serotonin reuptake inhibitors (SSRI’s), selective noradrenaline reuptake inhibitors (SNRI’s), gabapentin and pregabelin have also shown an improvement in flushing, whilst Vitamin E, evening primrose oil and acupuncture have been shown to be of no benefit. Black cohosh or any compound with estrogenic properties should be used with extreme caution in women with a history of breast cancer.

Vaginal atrophy almost always occurs as a result of estrogen deficiency, and it is the one symptom of the menopause that gets worse with time. The symptoms of dryness, burning and pruritis leads to dyspareunia, which often has a negative impact on all domains of the sexual response cycle. About a third of breast cancer survivors have moderate to severe vaginal dryness.

Topical estrogen treatment is the most effective therapy for vaginal atrophy. There is limited systemic absorption. Symptom relief was noted as early as 2 weeks after initiation of therapy on a daily basis for 14 days and then twice a week. It is best to start treatment early before irrevocable changes have been established. Symptoms will return on cessation of therapy.

Other therapies that are under investigation for the treatment of vaginal atrophy include intravaginal tamoxifen, intravaginal dehydroepiandrosterone sulphate, ospemifene tablets (newer selective estrogen receptor modulator), and vaginal moisturiser. The latter must be differentiated from vaginal lubricants which provide comfort during sexual intercourse, and are used at the time of coitus, similar to condom use. Moisturisers work by hydrating the vaginal mucosa, and some products are formulated to restore the acidic vaginal pH. The benefits of a vaginal moisturiser are related more to consistent use rather than formulation.

Androgens and the breast

The aromatase enzyme system present in breast stromal tissue can convert androgens into estrogens.
Therefore breast cancer concerns have always been part of the debate involving androgen therapy in women.

Presently there is no FDA approved androgen prescription product available for women. The use of male or bio-identical products is unregulated.

There is strong evidence that androgens influence female sexual function and that testosterone therapy may be useful for women who have experienced loss of sexual desire and/or arousal.4

In 29 patients who underwent female to male sex change, the histology of their mastectomy specimens showed no differences as far as histology and receptor status when compared to specimens from breast reduction surgery. Shufel and Braunstein’s5 writing in Menopause International in 2008, stated that “epidemiological studies, controlled for endogenous estrogen levels, showed either a decreased or no increased risk of breast cancer with testosterone therapy.”

The future may see another drug which has already been launched in Europe. It is a tissue selective estrogen compound which combines a SERM (selective estrogen receptor modulator) called bazedoxifene with conjugated equine estrogen. It has the potential to reduce vasomotor symptoms, improve vaginal health, decrease bone turnover while being neutral as far as the uterus, ovary and breast are concerned. Breast tenderness, vaginal bleeding and rates of endometrial hyperplasia are similar to placebo therapy. Cardiovascular and venous thrombotic events had comparable rates with placebo.6

The role of a multi-disciplinary team in the management of a breast cancer survivor is unquestioned, but the patients requiring specialised help have to be recognised and directed appropriately.

Primary care providers are at the forefront of providing survivorship care, and the 5 As framework provides a model for communication:2

1. **Ask** about sexual health in a non-judgemental manner and use open ended questions
2. **Advise** that help is available
3. **Assess** the problem
4. **Assist** by directing the patients to educational material, web sites and refer them to appropriate ancillary services.
5. **Arrange** follow up sessions so that patients realise that their issues are being taken seriously and the remaining challenges can be addressed.

**Conclusion**

Addressing the sexual health of breast cancer survivors and their partners is of fundamental importance. Cancer and its treatment have the potential of impacting negatively on sexuality. If the latter causes personal or couple distress, it needs to be managed in a non-judgemental fashion, irrespective of the age of the patient.

The quote by Sharon L Bober et al is most edifying: “for the majority of female cancer survivors, optimising sexual function can lessen emotional distress and improve psychosexual adjustment. Physical pleasure and emotional intimacy are life affirming experiences that can relieve stress and promote closeness and healing for both survivors and partners.”

**References**

NOFSA response to the article “Menopause Matters”
Menopause Focus Vol 4 No3, Aug 2016, 15-16

Dr Stanley Lipschitz, Dr Tobias De Villiers, Dr Michael Davey
on behalf of the National Osteoporosis Foundation of South Africa

The National Osteoporosis Foundation of South Africa (NOFSA) would like to comment in response to the opinion by Prof. Athol Kent in Menopause Matters as published in Menopause Focus which we feel is imbalanced and misleading in several domains.

The controversy raised by Menopause Matters mainly concerns two areas of contention, namely calcium and vitamin D supplementation and the use of pharmacotherapy to prevent fractures. These controversies are fundamentally based on two papers by Järvinin and Greg & Bollard.

Kent’s opinion paraphrases these articles extensively. The unfortunate part about his opinion is that he omits to report on published responses to these articles by respected sources such as the International Osteoporosis Foundation (IOF) (available on the NOFSA website www.osteoporosis.org), and thus does not allow the reader to formulate a balanced opinion. For the sake of scientific balance, we now address points raised by Menopause Matters.

1. “Better management of fractures” – NOFSA agrees with this and a joint publication by NOFSA and the South African Geriatrics Society (SAGS) offers local recommendations for patients who have suffered a fracture of the proximal femur.

2. “Prevention by lifestyle changes” – NOFSA agrees that “most hip fractures occur in people older than 75 years, many of whom are frail or have comorbidities”. By focussing only on hip fractures Kent greatly undervalues the total benefit of therapy for osteoporosis. Hip fractures constitute only a small percentage of total fractures due to osteoporosis and many of these fractures occur after extremely minor trauma. Spine fractures and non-vertebral non-hip fractures constitute the vast majority of insufficiency fractures in the elderly and are associated with considerable morbidity and even increased mortality. Falls prevention strategies should indeed form part of the clinical assessment of all older patients.

3. “Prevention by Osteoporosis Diagnosis and Treatment” – Kent states that “it is the trauma of the fall that causes the fracture of their fragile bones” and “it is the propensity to fall, not bone fragility that predicts fractures”. This begs the question of why babies who fall more than the elderly do not sustain fractures consequent to these falls. We differ from the author on the following basic principles:

   a. There is a clear association between low bone mass and fracture risk in post-menopausal women and older men.
   b. Other risk factors for fracture are important and should be included when assessing individual fracture risk. These risk factors (age, previous fractures, low BMI, smoking, excess alcohol, secondary osteoporosis, glucocorticoids, etc) have been included in various fracture risk algorithms including those advocated by NOFSA and FRAX.
   c. Randomised clinical trials (RCT’s) have consistently demonstrated efficacy at reducing fractures at spine, hip and non-vertebral sites. RCT’s serve as the gold standard for evidence based medicine.
   d. Compston addresses the claim that osteoporosis medications have not been proven to work in the elderly. She offers several explanations for this. In one study subjects were randomised based only on risk factors and not BMD. A second study was not adequately powered to demonstrate fracture efficacy in the older woman. In a third study hip fracture was not a primary endpoint. And a fourth study was grossly underpowered to demonstrate hip fracture efficacy. As stated by Compston “absence of evidence does not constitute evidence for absence of effect”.
   e. The aim of treatment is the prevention of all fragility fractures as stated above. Analyses from some of the pivotal studies have in fact shown efficacy in this regard in the older patient. Boonen et al analysed pooled data from RCT’s in women 80 years and older and showed an 81% reduction in new vertebral fractures in women treated with risedronate compared to placebo after only 1 year. Analysis of data from 3658 women treated with alendronate showed a consistent relative risk reduction for hip, spine and wrist fractures across all age groups. Boonen et al also showed significant relative risk reduction in all new clinical fractures (35%), clinical vertebral fractures (66%) and non-vertebral fractures (27%) in women >75 years on zoledronic acid compared to placebo enrolled on the Horizon trial.

4. As stated by IOF
   a. Osteoporosis is still alarmingly under-diagnosed and undertreated, even after a fragility fracture.
b. The elderly are particularly vulnerable where levels of diagnosis and treatment are lowest.

5. Like the IOF, NOFSA in its guidelines advocates a systemic approach to fracture prevention which includes lifestyle modification (stop smoking and reduce alcohol), good diet, exercise and fall prevention strategies.

6. The harsh reality however is that the vast majority of falls prevention programmes have failed to reduce fracture risk. The meta-analysis referred to by Kent which suggests that preventing falls can reduce fracture risk is inherently flawed in that most women on the study were under 75 years of age and many did not have risk factors for falling. Extrapolating this data to the frail elderly at high risk of falls and fracture is ill advised, as a simple exercise programme including advice to exercise or walk is extremely hazardous, and if not done under controlled conditions with expert guidance (biokinetics), will serve to increase the risk of falls and fractures.

7. Measures to prevent falls should be an integral part of a fracture prevention programme. However assertions that such measure are as effective or more effective in preventing fractures as pharmacotherapy is a misrepresentation of current evidence.

8. The potential of therapeutic harm is overstated by Kent. Patients with active upper gastrointestinal problems should not be prescribed an oral bisphosphonate. In other patients upper GI adverse events are extremely rare provided the drug is taken in the correct manner. Atypical fractures and osteonecrosis of the jaw (ONJ) are extremely rare complications in patients with osteoporosis treated for <5 years or when the recommended doses for fracture protection are used as apposed to the far higher doses used in oncology.

9. The Kent statement “there is harm in being treated with drugs of no proven benefit that are not cost effective and have known side effects” is inaccurate and misleading. An approach to fracture prevention which includes drug therapy has in fact been shown to be cost effective. Intervention thresholds based on clinical assessment and rational use of guidelines will allow appropriate and cost effective treatment of those at greatest risk of fracture.

10. Juliet Compston succinctly states “Editors of academic journals have a responsibility to ensure that published papers are balanced and reflect the available evidence”. This is true of a journal such as Menopause Focus, which is widely read by primary care practitioners and healthcare commissioners who cannot be expected to have in-depth knowledge of specialist topics. We agree with Compston that unbalanced opinions, such as that of Kent, do a disservice to the elderly who suffer fragility fractures and to the scientists and patient organisations that have worked tirelessly over many years to improve their management.

11. Osteoporosis, calcium & vitamin D – Updated guidelines regarding adequate calcium and vitamin D are available from IOF and NOFSA (www.iofbonehealth.org, www.osteoporosis.org). NOFSA does not advocate routine calcium or vitamin D supplementation. Calcium needs should be met via dietary sources if possible. Our updated guidelines recommend only supplementing calcium (maximum 500mg per day) in those who have osteoporosis or are at risk of fracture and who cannot or will not take adequate calcium in the diet. For vitamin D our guidelines recommend 800IU daily only for those who have osteoporosis or who are at high risk of fracture. The suggestion that doctors are prescribing calcium and vitamin D because of perverse incentives is firmly rejected by NOFSA. Doctors do after all prescribe anti-hypertensives, statins, diabetes medication, anti-depressants and menopausal hormone therapy, all of which are marketed and sold by the pharmaceutical industry. Is Kent suggesting that all pharmaceutical products are prescribed in a perverse manner?

References

Response to the article “Menopause Matters”, Menopause Focus Vol 4 No 3, Aug 2016, 15-16 - Letter to the editor

Dear Dr Moodley

**Re: Menopause Matters**

I guess from the tone of your Editorial you were expecting a robust response to Professor Athol Kent’s article on ‘Menopause Matters’. (Menopause Focus, August 2016).

As a gynaecologist who tries to provide evidence-based care and advice to the women in my care I found the article puzzling.

To prevent osteoporosis, Prof Kent advises women to stop smoking, exercise and eat well; interventions that are cost effective. I have many women who do the above and yet have osteoporosis: and those who don’t adhere to lifestyle advice, being obese junk food eating couch potatoes, don’t give a fig for my instructions. Whilst the advice is intuitively sound, it is the language of perfection in an imperfect world. What of the women with existing osteoporosis? What do we offer those unfortunates? He makes no mention of estrogen and combined estrogen/progesterone therapies which safely prevent the development of postmenopausal osteoporosis and osteoporosis-related fractures, at both the spine and the hip.

Prof Kent continues that recent revelations that bisphosphonates do not prevent fractures, and evidence that vitamin supplementation is, on balance, harmful, should prompt us to reflect on our management when ordering tests or advising treatment. He suggests that we collude with drug companies when prescribing supplements to patients (Does a tissue box of Fosavance tissues amount to collusion?). Prof Kent panicked me when I read that the potential harms caused by bisphosphonates include atypical femoral fractures and osteonecrosis of the jaw (ONJ). A quick google shows that in clinical practice ONJ is extremely rare at the dosages of bisphosphonates used for fracture protection, and is more commonly related to much higher dosages of bisphosphonates used in oncology.

Regarding atypical fractures of the femur shaft (AFF), bisphosphonates reduce the risk of femur neck fractures. After 3 – 5 years of bisphosphonate therapy, a possible relationship with fractures of the femur shaft has been observed, although a direct causal effect has never been proven. If bisphosphonates are used for periods of more that 3 – 5 years, the number of prevented femur neck fractures still far outnumber the possible AFF’s caused.

I glanced through the reprint “Current Osteoporosis Management” from Current Care of April 2015 which quotes the NOFSA guidelines.

It is apparent that these guidelines and the paper by Prof Kent, are poles apart. For the average gynaecologist who is not a menopause specialist, our minds are in academic confusion in a sea of uncertainty. I am not sure that “lifestyle advice” will placate all women with osteoporosis – I am sure it won’t mollify my patients. If they hear that bisphosphonates don’t prevent fractures, and that supplements are harmful, I would be in hot water.

The fact that a few author’s views published in prestigious journals find resonance with Prof Kent’s own thoughts, are insufficient to trash a large body of opinion, and throw the baby out with the bathwater. There are many good examples of irrationality published in mainstream journals – such as the WHI which had several strange conclusions causing widespread suspension of HT, and Wakefields 1998 publication in Lancet regarding autism and MMR vaccination.

Let’s wait for the jury to return before the medical profession blows with the flatus of change.

Yours Sincerely

Peter de Jong
A

other year has gone by, as has the term of office of the SAMS Council. Nominations have been received for the new Council and it looks like an election will be unnecessary. The new Council will be announced at the SAMS annual general meeting to be held on the 26th November during the SAMS 2016 conference.

The following members of the present Council have chosen not to stand for election again:

It is impossible to thank these Council members adequately for their long term commitment to the South African Menopause Society as well as the health and well being of the maturer woman. They have all set very high standards in providing appropriate and scientifically sound advice for those women who pass the menopause and face often unpleasant symptoms and also other health risk factors. We wish them all well, but know they are all people who will not withdraw completely from this field and I am sure we will need to call on their expertise from time to time.

Percy Moodley has successfully guided Menopause Focus through this year and at last we are seeing the fruits of his efforts to stimulate debate around issues which face us as practitioners caring for post menopausal women. We hope that you join the debate and look back carefully at the last issue in order to compare those points raised by Menopause Matters and compare them with those of NOFSA and the letter to the editor. It is indeed sometimes confusing and difficult to decide what is appropriate, ethical and safe treatment for our patients. We hope that Menopause Focus is able to assist you in making sound decisions.

As I shall be handing over the Presidency of SAMS to Carol Thomas at the AGM in November, I would like to thank all the Council Members who have given me support during the last 20 months. Included in those Council Members are Alan Alperstein, Tobie de Villiers, Carol Thomas, Johannes van Waart and Paul Dalmeyer who have done fantastic work in helping arrange the SAMS 2016 conference. The program is appropriate for all healthcare providers who look after women at menopause and beyond, whether they be general practitioners, women’s healthcare practitioners or gynaecologists. We have also made a special effort to register some of our trainees from the rest of Africa at a special price so that they can take some of the information available through this very informative conference back to their countries, such as Malawi, Botswana, Kenya, Uganda, Ghana and some others.

We hope to see as many of you as possible at the SAMS Conference 2016 and if not, wish you all the best for the remaining months of the year and a fantastic start to 2017.

Peter Roos

---

**SAMS Mission Statement**

The South African Menopause Society (SAMS) is one of South Africa’s leading nonprofit organisations that is dedicated to promoting women’s health during midlife and beyond, through the understanding of menopause. It boasts a membership of over 190 leaders in the field (including clinical and basic science experts from medicine, nursing, sociology, psychology, nutrition, anthropology, epidemiology and education). This allows SAMS to be the dominant resource on all aspects of menopause to both healthcare providers and the public.

**Become a SAMS Member today and enjoy the benefits:**

- Monthly Electronic Newsletter Menopause Matters
- Bimonthly faxed Newsletter News by Fax
- Menopause Focus every 3 months
- Regular scientific meetings featuring acknowledged experts in the field
- Discounted registration fees at SAMS conferences
- Guidelines and updates on international menopause related issues

SAMS boasts a multidisciplinary membership of menopause experts from diverse healthcare fields. Join SAMS to keep up to date with developments in this field.

Membership fee is R120 per annum. Contact the SAMS Secretariat at: info@menopause.co.za or call Alison Shaw on 082 5538201 for more details.
Finding the right pill can take longer than finding the right man.

Qlaira® delivers a derivative of natural estradiol in unique combination with dienogest. Suitable for women 18-50 years of age, Qlaira® offers benefits beyond contraception:

- The shortest hormone free interval – improvement of HWaS including pelvic pain and headache
- First oral contraceptive that delivers 17β-estradiol
- Lowest impact on haemostatic markers and liver metabolism
- Good cycle control, with short and light menstrual bleeding
- Improved sexual functioning

References:

For full prescribing information, please refer to the package insert approved by the Medicines Regulatory Authority.

Qlaira® Tablets. The 28-day pack contains 2 tablets each containing 3 mg oestradiol valerate and 5 tablets each containing 2 mg oestradiol valerate and 2 mg dienogest and 17 tablets each containing 2 mg oestradiol valerate and 3 mg dienogest and 2 tablets each containing 1 mg oestradiol valerate and 2 placebo tablets. RSA Reg. No.: 43/18.8/05. Namibia Reg. No.: 1521.8.20/154.

Bayer (Pty) Ltd. Reg. No.: 1968/11183/07. 27 Wrench Road, Isando, 1609. Tel. +27 11 921 5000.

Science For A Better Life

In harmony with a woman’s body
Help her make the smart choice until she's ready for motherhood by prescribing oral contraceptive YAZ®

YAZ® is the only COC* with 3 registered indications:1

- Oral contraception
- Treatment of moderate acne in women seeking oral contraception
- Treats symptoms related to PMDD** in women who have chosen oral contraception as their method of birth control

* Combined Oral Contraceptive
** Premenstrual Dysphoric Disorder. The efficacy of YAZ® for PMDD was not assessed beyond 3 cycles. YAZ® has not been evaluated for the treatment of Premenstrual Syndrome (PMS).