Relief from the symptoms of PERIMENOPAUSE\(^1\)

Significantly reduces the incidence of hot flushes\(^1,2\)

Treating the symptoms of POSTMENOPAUSE\(^2,3\)

Femoston conti\(^2\) significantly increases BMD in the lumbar vertebrae and hip trochanter\(^3\)

MENOPAUSAL HEALTH

References:
3. Stevenson JC, Teter P, Lees B. 17β-Estradiol (1 mg/day) continuously combined with dydrogesterone (5, 10 or 20 mg/day) increases bone mineral density in postmenopausal women. Maturitas 2001;38:197-203.

BMD = bone mineral density
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Editorial Board

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

Professor Franco Guidozzi
Academic Head, Chief Specialist, Dept of O&G and Medical School of University of Witwatersrand, Johannesburg

Professor Alan Alperstein
Gynaecologist
Kingsbury House, Claremont, Cape Town

Professor Jay Bagratee
Dept of Obstetrics & Gynaecology
Nelson R Mandela School of Medicine
University of KZN

Dr Paul Dalmeyer
Part Time lecturer at UCT, Obstetrician/Gynaecologist/Reproductive Specialist
Cape Town

Dr Tobie de Villiers
President of the International Menopause Society,
Gynaecologist in Private Practice
Cape Town

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Gynaecologist
Netcare Park Lane Hospital, Johannesburg

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Principal Specialist, Dept of O&G,
Charlotte Maxeke Johannesburg Academic Hospital and University of Witwatersrand
Johannesburg

Dr Johannes van Waart
Fertility Specialist in Private Practice
Wijnland Fertility Unit, Stellenbosch

DISCLAIMER: The views expressed by the editor or authors in this newsletter do not necessarily reflect those of the sponsors, the publisher or SAMS.
Taking over as Editor of Menopause Focus from Professor Franco Guidozi is indeed a daunting task. Over the past two years, under Franco’s guidance, Menopause Focus has produced excellent articles, satisfying both those with an academic interest and those needing helpful information to use within their clinical practices. During this time, he also completed the task begun by Professor Alan Alperstein, in producing the guidelines for the use of hormone therapy in South Africa. This was a massive task and Franco managed to get them published both in Menopause Focus and the South African Medical Journal.

Professor Guidozi needs to be thanked, not only for his role as Editor of Menopause Focus and President of the South African Menopause Society, but also for his contribution to women’s health in many other fields. His promotion of women’s health issues to both his students and colleagues has been much appreciated by the medical community in South Africa.

In this issue, the article by Professor Zephne v.d. Spuy on polycystic ovarian syndrome, highlights the fact that menopause is just the approximate midpoint in a continuum of health issues affecting women from youth to old age. She highlights the need for young women who are diagnosed with polycystic ovarian syndrome to have careful health surveillance for the rest of their lives. They need to be put on programs highlighting lifestyle changes, possible medication and long term surveillance of particularly such things as blood sugar, cholesterol and hypertension. She also makes the point that polycystic ovaries on ultrasound scan is not the only criteria required for the diagnosis of polycystic ovarian syndrome. She points out that although 20-22% of women have polycystic ovaries on ultrasound, only 5 – 10% of women of reproductive age develop the polycystic ovarian syndrome. As important as it is for long term health to make the accurate diagnosis of polycystic ovarian syndrome, so is it important not to over diagnose this condition in young women with ultrasound changes, but without either of the other two criteria (Rotterdam criteria). This frequently causes unnecessary anxiety about fertility and long term health in young women and their mothers.

Dr Mike Davey has produced an excellent summary of the efficacy and safety of Bisphosphonates available in South Africa. This goes a long way to reassuring practitioners and helping them provide answers for their patients. He points out that all Bisphosphonates available in this country are efficacious in fracture prevention and that the concerning side effects of osteonecrosis of the jaw and atypical femoral fractures are in fact quite rare and often related to the dose and duration of treatment.

Professor Franco Guidozi has once again produced a fascinating article examining some of the basic science behind sleep disturbances. This highlights the objective and subjective sleep disturbances which differ between men and women. Helping women and perhaps even their husbands understand the underlying neuro-endocrine causes for sleep differences will help them in managing their lives and perhaps this understanding will help reduce tensions in family and maybe even reduce the amount of hypnotics used by women to achieve more satisfactory sleep.

On the subject of osteoporosis, Peter Roos has highlighted the need for important general measures to prevent falls and thereby hopefully prevent fractures. A lot of time is spent on investigations and medical therapy for osteoporosis, but in clinical practice we tend to neglect the fact that it is quite simple to identify the risk of falling in older people. Once, having identified these risks, there is evidence that interventions are helpful in reducing falls and thereby fractures.

Not everybody who reads Menopause Focus is a member of the South African Menopause Society. We have therefore included a few short articles, which are sent to members of the South African Menopause Society on a regular basis, either by fax or e-mail. News by Fax is a one page summary of a topic which is of relevance to medical practitioners in their clinical setting. These one page articles are easy to read and are prepared by people with a specific interest in menopausal health. In this issue, we have an article concerning vaginal lubricants in older people and another on the use of hormone therapy in high risk patients.

Menopause Matters is e-mailed to members of the South African Menopause Society. These are prepared by Professor Athol Kent who has an international reputation for his Journal Article Summary Service (JASS). Professor Kent is an expert at searching the literature to find relevant articles to present to his colleagues. He is frequently controversial in his opinions about what might be called “standard practice”. His articles are always worthwhile reading.

By joining the South African Menopause Society, you would gain access to these interesting articles. Membership of the society is at present R150 annually. You can easily join by going to the South African Menopause Society Website and follow the links.
Polycystic Ovary Syndrome in the older woman

Professor Zephne van der Spuy
Emeritus Professor/Senior Scholar
Department of Obstetrics and Gynaecology, University of Cape Town

The polycystic ovary syndrome (PCOS) is the commonest endocrine condition among women in their reproductive years. It presents with variable clinical features and has a heterogeneous endocrine profile. PCOS usually presents with a patient complaining of reproductive symptoms such as hirsutism, menstrual disorders or infertility, but already at a young age there is evidence of metabolic disturbances. It is the metabolic dysfunction which poses a considerable health risk to women in their later decades.

Studies which have tried to assess the prevalence of PCOS have demonstrated polycystic ovaries, as assessed on ultrasound, in some 20-22% of women. Not all of them will develop PCOS as it only occurs in some 5-10% of women of reproductive age. Long term follow up is essential because of the possibility of ongoing metabolic disorders which may impact the health of affected women in later life. These include disorders of glucose tolerance and cardiovascular function.

Diagnostic criteria

Originally a 1990 NIH-sponsored conference on PCOS developed clinical criteria for diagnosis. It was, however, subsequently recognised these were narrow, did not include the use of ultrasonography which is central to assessing the morphology of the ovaries and needed review. As a consequence, in 2003, the Rotterdam Consensus Workshop which was an ESHRE/ASRM cooperative with independent funding brought together experts from around the world to develop guidelines for the diagnosis of PCOS. This workshop resulted in new standardised criteria for the diagnosis of PCOS which included the necessity for at least two of three criteria to be fulfilled before making the diagnosis of PCOS. (Table I and Table II)

Health-related quality of life (HRQOL)

Recent research has made it clear that HRQOL is often impaired in women with PCOS. A number of very good studies have indicated that women with PCOS have particular problems with regard to their body image, their relationships and their attitude to fertility. We need to recognise that PCOS is a medical condition which is complex, has immediate and long lasting health implications and in addition provides psychological challenges to affected patients. Ongoing health related practices must take this into account.

Implications for later life

It is difficult to determine why a woman with polycystic ovaries eventually develops PCOS. PCOS tends to cluster in families and it is therefore likely that there is a genetic element to this condition. In the debate between inheritance versus adverse environment, it is recognised that the environmental impact on the development of PCOS is very important. Intra-uterine stressors, events in childhood/puberty and the impact of obesity in adulthood may all influence the development of PCOS. In short, the metabolic environment may impact upon a woman’s genetic predisposition and result in the development of PCOS.

Subsequent to this consensus workshop we have all been encouraged to use the Rotterdam Criteria, both in diagnosing PCOS in our clinical practice and in all research endeavours to ensure universal recognition of a woman with PCOS. There has been considerable debate about this and some concerns that PCOS should only include women with hyperandrogenism. At present, however, the Rotterdam Criteria seem to be the best definition available and studies which use these criteria will be comparable and improve interpretation of research information.
There is considerable evidence that women with PCOS may later develop dyslipidemia, impaired glucose tolerance (IGT) or type II diabetes, the metabolic syndrome and ultimately these impact on cardiovascular disease (Table III). Both the diabetic related conditions and the cardiovascular factors result in an increased risk for cardiovascular disease and long term morbidity. There is considerable information in the literature about the possible impact of PCOS on late onset disease. (Table IV).

Norman et al (2001) reported that among women with PCOS who initially had a normal glucose tolerance test and were reassessed after six years, 9% had IGT and 8% had developed diabetes. In contrast, of those who had IGT at baseline, in the later assessment 54% of them were diabetic. This statistic demonstrates the need for ongoing surveillance of women with PCOS during and after their reproductive years.9

In terms of cardiovascular disease, there is some debate as whether PCOS itself impacts on patients or whether this has been over-interpreted.10,11 In the past few decades there have been some very important studies reviewing this risk. A study from Denmark, authored by Dahlgren and her co-workers (1992) presented long term follow up of women who had wedge resections for PCOS. They reported that hypertension occurred in 39% of patients versus 11% of the controls and diabetes in 15% of patients versus 2.2% of the controls. There was often a strong family history of diabetes and cardiovascular disease in the PCOS patients. All of this suggests that PCOS patients are at increased risk of cardiovascular and diabetic disease.12 The family history is important but the diagnosis of PCOS adds to the risk status. A more recent longer follow up study by Dahlgren and her co-workers indicated a higher prevalence of hypertension (p=0.008) and higher triglycerides levels among PCOS patients than controls (p=0.012). There was no significant increase in cardiovascular events.13

Pierpoint and his colleagues reviewed women who had been diagnosed with PCOS through ovarian biopsy from 1930 to 1979. This group of women from Oxfordshire had a death rate which was comparable with national rates. There was no excess mortality from cardiovascular disease, but diabetes-associated deaths were increased in this group. It is important to note that this study was done in a very well-resourced healthcare environment and morbidity was not assessed. The authors suggest that raised oestrogen levels in PCOS may be cardio-protective but that the insulin resistance leads to diabetic problems.14,15

This information leaves us with the problem of counselling women who are diagnosed with PCOS when they are young about how they should be followed up and which therapy is essential. Reviewing the current literature, it is suggested that all women with a BMI of 25 or higher need to have a GTT and if this shows any abnormalities at all, annual follow up should be arranged. Women whose BMI is <25 and who have additional risk factors such as age, previous gestational diabetes or a family history need annual follow up. In addition any patient with IGT needs to be assessed in a follow up programme.16

### Cardiovascular disease

It is evident from the literature that conventional cardiovascular disease (CVD) risk calculators have never been validated in the PCOS population. This obviously presents a problem in counselling patients and also offers potential areas of future research.

It is recommended that hypertension should always be appropriately managed and that statins may need to be introduced if indicated. There is considerable disagreement as who should receive statins and how early this should be added to therapy. Some studies among adolescents from the USA suggest statins may well be introduced to very young patients together with insulin sensitising agents. In contrast, studies from Europe and Australia are less enthusiastic about this option.

The publication by Birdsall et al reported that women who presented with chest pain and had cardiovascular assessment through angiography, had a greater degree of vascular damage among those who were diagnosed in the post-menopausal years with PCOS than those who do not have PCOS. This obviously is an indication for ongoing assessment and outlines the importance of monitoring a woman with PCOS in later life.17

### Psychological impact

There is a growing literature on the health-related quality of life in women with PCOS. Depression and problems with their health conditions have been demonstrated in women with PCOS. Well validated tools for assessing health-related quality of life have been developed and may be useful in clinical practice.7

Our current recommendation would be that every woman we diagnose with PCOS be carefully counselled and get ongoing care if the clinician feels this is indicated. We need to recognise that many of these patients have a poor body image, are depressed, struggle to cope with their unrealised fertility aspirations and worry about their future health. They need support and ongoing input, ideally from a multi-disciplinary team.
Cancer

Neither breast cancer nor ovarian cancer seems to be adversely affected by PCOS. There is, however, extensive evidence indicating that inappropriate endometrial stimulation secondary to anovulation, as seen in PCOS, may result in endometrial hyperplasia and eventually cancer. This has been well-documented in young women with PCOS and endometrial surveillance must be central to the management of all patients.7,8

Ongoing therapeutic challenges in the older woman: (Table V)

The older woman presents with particular challenges. Firstly, as is outlined in the most recent consensus statement from the ESHRE/ASRM-sponsored workshop in Amsterdam, the diagnosis of PCOS in post-menopause is difficult and often depends on previous clinical markers such as oligomenorrhea.

There are little data on the age of menopause in PCOS but there is evidence that age may well improve menstrual function. Cycles tend to regulate in later life possibly because of the decrease in follicles and therefore reduced abnormal ovarian endocrine function.18

The challenges of PCOS when managing older women continue. We need to address their long term healthcare which includes glucose intolerance, diabetes, hypertension, dyslipidemia and ultimately cardiovascular disease. This requires long term monitoring and patients need to understand that once they are diagnosed, they need to be part of an ongoing therapeutic programme.20

Women may present in their forties wanting ongoing treatment for hirsutism and this presents problems as therapeutic options are limited given the many medical problems that may be present. We need to assess what therapy is available for the older woman. If hirsutism is a problem then we are limited to spironolactone which can act both as a diuretic in hypertensive therapy and an anti-androgen. Many of the options for treatment with cyproterone acetate are not available to the older woman because of other risk factors. Cosmetic therapy is important and should be accessed but often is expensive and not universally available.

Long term monitoring

Patients need to be carefully counselled about the long term options for them and the possible clinical and medical problems which may present. Treatment protocols need to be individualised and it is essential that there is a referral protocol for all patients with PCOS who have metabolic problems.

Lifestyle changes and addressing the challenges of obesity may significantly contribute to improved management.

Therapy with metformin and other insulin sensitisers may be helpful but this treatment option is still not clearly resolved.16,19

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Conclusion

In conclusion, PCOS remains a challenge and a fascinating condition. While most patients present in their reproductive years, often because of menstrual abnormalities or infertility, many only present in their late thirties or early forties and all will need treatment and surveillance into later life.

The high risk of developing diabetic complications and the cardiovascular risk factors are emphasised in most research publications. We need to counsel patients who are diagnosed with PCOS as young women, that this is an ongoing condition and that follow up is essential. We can optimize management and it is important that our counselling makes them understand the need to comply with treatment.

References

Sleep and gender

Professor Franco Guidozzi  FCOG, FRCOG
Department of Obstetrics and Gynaecology
University of the Witwatersrand.

In recent years, increasing attention has been given to understanding the association of gender with sleep health. Sleep patterns are sexually dimorphic in several species. Human and animal studies have shown that gender and gonadal hormones do influence the circadian and homeostatic processes although it remains unknown whether the gender associated differences in the sleep/wake cycle are mediated by either or both of these processes. Secretion of the gonadal hormones, estrogen, progesterone and testosterone, have two primary effects: organizational and activational, and it is at the time of birth that they play their major role in organising the neural circuitry responsible for gender differences in behaviour later in life, including sex specific mating behaviour, aggression, arousal and stress responses.

Sex influences brain anatomy, chemistry and function. The impact is not only confined to birth but the functional differences will continue to develop and emerge as the gonadal hormones act on the differentiated circuitry across puberty and adulthood. Having said this, however, while much is known about the mechanisms of sleep and circadian timing, the knowledge of sex differences and gonadal hormonal impact on sleep/wakefulness is in its infancy.

The supra-chiasmatic nucleus (SCN) has estrogen receptors adding to the concept that the effects of the gonadal hormones, and possibly sleep, could be through their action on the estrogen receptor containing SCN neurones. It appears that estrogen receptor mRNA levels show a diurnal rhythm raising the possibility that the effects of estrogen on the sleep/wake cycle could be influenced by such diurnal variations. It has also been shown that the SCN extends projections to estrogen receptor immune-reactive neurones and that estrogen receptor neurones project to the SCN.

Although the interaction of gonadal hormones with the sleep/wake cycle is complex, studies in humans have shown sex differences. Women have twice as many spindles, more slow wave sleep, a higher sleep drive, a differential time course in delta activity and a slower age-related decline in delta compared to men. There is information on sex differences in other species. Male rats have more REM sleep than females throughout the light/dark cycle and age-related changes in slow wave activity are present in cats with faster age declines in delta in males compared to females.

In the human population, clinical evidence indicates that men and women sleep differently. Women spend more time in bed and sleep longer, but report a poorer sleep quality than men. Women are significantly more likely to report sleep disturbances including difficulty in falling asleep, staying asleep, early morning wakening or insufficient sleep compared to men. Despite women being more likely to report their sleep having the abovementioned features, objective analysis with polysomnographic analysis of sleep architecture has not substantiated these complaints. Women have less wakefulness after sleep onset, less stage 1 sleep, more slow wave sleep and more slow wave activity during their sleep compared to men.

Estrogen receptors have been located in the medial preoptic nuclei, the medial cell groups in the hypothalamus, medial limbic forebrain structures such as the medial amygdala and the lateral septum and the hippocampus. Estrogen, like progesterone, alters neuronal excitability through its interactions with gamma-aminobutyric acid and 5-HT receptors, increases turnover of norepinephrine in brainstem, hypothalamus, locus coeruleus and appears to decrease REM sleep significantly in animal studies. Data in humans comes from placebo controlled trials where estrogen therapy is administered to peri- and postmenopausal and the findings support that estrogen decreases latency to sleep onset, decreases wakeful after sleep onset, increases total sleep time and decreases rate of cyclic alternating patterns. Estrogen in humans appears to affect REM sleep but not NREM sleep enhancing effect on REM sleep with increased time spent in REM sleep and decreased latency to REM sleep. As in animal studies, in humans, progesterone and some of its metabolites, particularly pregnanolone, exhibit sleep promoting effects that are generated by progesterone’s actions as a GABA receptor agonist. Progesterone increases NREM sleep, decreases slow frequency range (0.4-4.3 Hz) and increases higher frequency range (> 15 HZ), actions that are very similar to those of benzodiazepines. Androgens appear to have mild positive influence on REM sleep and seem to induce sleep apnoea onset in men and women.

Other perspectives which substantiate sex differences in sleep include facts such as women going to bed earlier than men from childhood to menopause following which the sex differences are no longer seen, sleep-debt accumulating occurring more quickly in women and the fact that women have higher levels of short wave activity during baseline sleep and a greater short wave activity rebound following sleep deprivation compared to men.
Few population based data are available to estimate the variation in sleep architecture across the population. There is information coming out of the Sleep Health Heart study that has been accumulating patients for a number of years which does provide very interesting data. Cross-sectional analyses of 2685 participants, aged 37-92 years of age in a community-based multicentre cohort study in which sleep was assessed by polysomnography coupled in the analyses with covariate data describing host and environmental factors that may affect sleep supports that sleep is clearly impacted by age and sex/gender. After adjusting for all other significant factors, poorer sleep architecture as measured by increased percentage stages 3 and 4 and REM sleep, lower sleep efficiency and a higher arousal index was found in men compared to women. In fact, for all measures other than the arousal index, gender explained the largest proportion of variance in each parameter measured with view to sleep architecture. In the overall sample, increasing age was associated with indices of poorer sleep architecture, as measured by decreased REM sleep, decreased sleep efficiency and increased arousal rates. The possible reasons for the changes in sleep architecture that occur in men with aging, with specific reference to the significant decrease of stage 3 and 4 sleep, may be due to age-related reductions in cortical mass, cortical metabolism or neurotransmitter levels, changes in circadian rhythms or other neuroendocrinological activity. Sleep characterized by frequent awakenings, arousals and less slow wave (delta or stage 3 and 4) sleep is considered to be lighter or non-restorative, resulting in daytime sleepiness. Interestingly the likelihood of daytime sleepiness according to sex was not clearly substantiated in this analysis.

This study again clearly substantiates the very different perceptions amongst women with particular reference to subjective appreciation versus objective analysis of sleep architecture. Women are significantly more likely to report sleep symptoms including difficulty in falling asleep, staying asleep, early morning awakening or insufficient sleep compared to men. Daytime sleepiness is often the result of nocturnal sleep problems, such as sleep disordered breathing, insomnia and the restless syndrome. Daytime sleepiness has been associated with poorer health outcome and quality of life, poor cognition, greater limitation in instrumental activities of daily living and higher rates of work and motor vehicle accidents. Simply because women perceive to have greater sleeping difficulties, the amount of use of hypnotics among women is greater than that amongst men.

Despite the studies reporting a trend in women of describing more daytime sleepiness than in men, there is still significant controversy as to whether this is the situation and future studies will need to explore more thoroughly the different ways men and women describe their daytime sleepiness experiences that are free of sex and ethnic differences and determine any associations between these subjective reports and objective measures of associated sleepiness.

Studies of sex differences in the timing of human circadian rhythms have reported conflicting results. A recent analysis showed that sex differences in the timing of circadian rhythms between males and females are evident. In the study, 28 women and 28 men maintained a regular sleep wake schedule of their choice at home and after 3 baseline days in the laboratory participants began a constant routine. Women were found to have a significantly higher melatonin amplitude and lower temperature amplitude than men. While sleep timing was the same between the 2 groups, the timing of the circadian rhythms of core body temperature and pineal melatonin secretion was earlier relative to sleep time in women as compared to men. Sleep therefore occurred at a later biological time for women than men, despite being at the same clock time. Given that sleep propensity and structure vary with circadian phase and are impacted by circulating melatonin, these findings may have important implications for understanding sex differences in sleep timing and duration.

There are a number of studies in rodents which have addressed the issue of sex and female gonadal hormonal impact on sleep with evidence to support that gonadal steroids modulate wake-sleep patterns, primarily through their impact on NREM and REM sleep and their impact on the circadian and homeostatic sleep responses, circadian rhythms acting through the many estrogen and progesterone receptors in the brain, with particular emphasis on these receptors in the preoptic area, the ventrolateral preoptic area and the suprachiasmatic nucleus. Estradiol inhibits activation of sleep promoting ventrolateral preoptic area, and gonadal steroids may affect circadian rhythm and subsequently sleep via direct modulation of the suprachiasmatic nucleus functions. Androgen receptors are prevalent in the suprachiasmatic nucleus with mounting evidence which demonstrates that androgens act directly in the suprachiasmatic nucleus to modulate circadian rhythms in mice, possibly by altering responses to light. The important question of whether men and women sleep differently is due to gonadal hormonal modulation only or whether there are inherent sex differences has still not been defined. It seems that in mice both hormone dependent and independent components are involved although it does appear that the sex differences in sleep-wake amount, distribution and intensity are dependent upon the presence of gonads. Female mice have 90 minutes a day more wakefulness, more consolidated sleep-wake patterns with less arousals from sleep during their quiescent phase and more wakefulness during their active period than males, all at the expense of NREM sleep.

Another perspective where sex differences are apparent is when one considers sleep disorders of which the most common include insomnia, sleep related breathing...
disorders, notably obstructed sleep apnoea, circadian rhythm disorders including delayed sleep phase disorder (DSPD), advanced sleep phase disorder (ASPD) and sleep related movement disorders, including restless legs syndrome, periodic limb syndrome. Sleep disorders are common and do occur in both males and females, but again the disorders reflect that sleep is different in men compared to women and accordingly the prevalence rates of these disorders differ somewhat between men and women. Compared to men, women report symptoms of insomnia at least a few times a week, particularly with view to more difficulty in falling asleep, more difficulty in maintaining sleep, having more sleep arousals and having more trouble returning to sleep, feeling less rested, sleeping less over weekends and more daytime sleepiness. On the other hand, men report more snoring or apnoeic spells than women. Sex differences with view to sleep are not only subjective. There is also objective evidence to support these differences. In a meta-analysis of 65 studies which included 3577 patients from 5-102 years of age sleep architecture was assessed by polysomnography and two important set of data came from this study:

A. In adults, total sleep time, sleep efficiency, percentage of SWS, REM and REM latency significantly decreased with age, whilst sleep latency, percentage of stage 1 and 2 sleep and wake after sleep onset significantly with age for both men and women.

B. The association between sleep variables and aging were very similar for both sexes. However larger effect sizes were observed in women for total sleep time and sleep efficiency, indicating that the age effect on these variables were more important in women. Further analysis indicated that women had longer TST and sleep latency than similarly aged men, less percentage stage 2 sleep and greater percentage of SWS.

References

Review of the efficacy and safety of the bisphosphonates available for the treatment of osteoporosis in South Africa

Dr Mike Davey MB BCh, FCOG(SA)
Private obstetrician/gynaecologist, Westville Clinic, KwaZulu-Natal, South Africa

The bisphosphonates have been available in South Africa for over 20 years and remain the class of drugs most widely used to treat patients with osteoporosis. This review will focus primarily on the results from the pivotal fracture studies using the bisphosphonates that are currently registered for the treatment of osteoporosis in South Africa and will discuss the side effects of this class of drugs in general.

Structure and Mode of Action

All currently used bisphosphonates are nitrogen containing bisphosphonates characterized by a nitrogen containing side chain. Presently available are the oral agents, alendronate and risedronate, and the intravenous agents, zoledronate and ibandronate. At the core of all bisphosphonate molecules is a P-C-P bond which is extremely resistant to hydrolysis and therefore biological degradation. This is one of the reasons for their long biological half-life.

The bisphosphonate molecule binds strongly to bone mineral, both hydroxyapatite and carbonated apatite. The acidic environment created on the surface of the bone by the osteoclast results in release of the bisphosphonate molecule which is taken up by the osteoclast where the it inhibits both function and survival of the osteoclast by inhibiting farnesyl pyrophosphate synthase (FPP synthase) and thereby disrupting the mevalonate pathway.1 The potency of the antiresorptive action and the duration of action of the bisphosphonate is determined both by the degree of binding to bone mineral and the strength of action on FPP synthase. By virtue of the above actions, alendronate and zoledronate would be considered more potent and longer acting antiresorptives than risedronate and ibandronate.

Efficacy of the bisphosphonates

Alendronate

Alendronate is the most widely used oral bisphosphonate worldwide and presently in South Africa is administered as a 70mg weekly oral dose. The pivotal fracture study was the Fracture Intervention Trial (FIT). In this study patients were aged 55-81 years and had T-scores of ≤ -2.1. In patients with previous vertebral fractures2 there was a significant reduction in both morphometric vertebral fractures (RR 0.53 CI 0.41;0.68) and hip fractures (RR 0.49 CI 0.25;0.99) (Fig 1). In patients without vertebral fractures3 there was again a reduction in vertebral fractures (RR 0.56 CI 0.39;0.80) but there was no reduction in either hip fractures (RR 0.79 CI 0.43;1.44) or non-vertebral fractures (RR 0.88 CI 0.74;1.04) (Fig 2). It is important to realize that the patients in FIT had T-scores of ≤ -2.1 according to the old NHANES reference data which were in use at the time of randomization. If the currently used NHANES3 data had been used the T-scores would have been ≤ -1.6. Many of these patients without fractures would therefore not have qualified for treatment according to current guidelines.

A Cochrane review4 of 11 studies, 3 of these primary prevention studies and 8 secondary prevention studies,
concluded that there is evidence supporting the efficacy of alendronate in the primary prevention of vertebral fractures and the secondary prevention of vertebral, non-vertebral and hip fractures.

Due to recent concerns about long-term safety, attention has focussed on the issue of how long to treat patients with bisphosphonates. In the FIT long-term extension study (FLEX)\(^5\) 1099 patients who had been on the FIT study for between 3 and 4.5 years were randomized to continue with alendronate 10 mg daily for a further 5 years or to placebo. In the group on active medication there was a significant reduction in clinical vertebral fractures but no reduction in morphometric vertebral or non-vertebral fractures when compared to placebo.

**Risedronate**

Risedronate is available in South Africa as a 35mg weekly oral tablet. The pivotal fracture studies were the VERT and HIP studies (fig 3). In the VERT study\(^6\) all patients had previous vertebral fractures on randomization. At 3 years the patients on risedronate had a 41% lower incidence of vertebral fractures (RR 0.59 CI 0.41;0.68) and a 49% lower risk of non-vertebral fractures (RR 0.61 CI 0.39;0.94). In the HIP study,\(^7\) patients had T-scores of \(\leq -4.0\) or \(\leq -3.0\) with additional risk factors for fracture. There was also a group of patients who were recruited into this study on the basis of risk factors alone. In the overall group there was a 30% reduction in the risk of hip fractures in the patients randomized to risedronate (RR 0.70 CI 0.60;0.90). In the patients aged 70-79 years the reduction in fracture risk was 40%. There was no significant reduction in hip fractures in the patients randomized on the basis of risk factors for fracture alone. A Cochrane review\(^8\) of 7 studies, 2 primary prevention and 5 secondary prevention studies, concluded that there is evidence supporting the efficacy of risedronate in the secondary prevention of vertebral, non-vertebral and hip fractures.

**Zoledronate**

The high incidence of upper gastro-intestinal symptoms and the lack of compliance with the use of oral bisphosphonates makes the use of intravenous preparations an attractive option. The pivotal fracture study using zoledronate was the HORIZON study.\(^9\) All patients in this study had T-scores of \(\leq -2.5\) or \(\leq -1.5\) with either 1 moderate or 2 mild vertebral fractures. This would make this cohort of patients typical of the profile of osteoporosis patients who would receive osteoporosis in the clinical situation. In patients randomized to a yearly 5mg infusion of zoledronate there was a 70% reduction in vertebral fractures (RR 0.30 CI 0.24;0.38), a 25% reduction in non-vertebral fractures (RR 0.75 CI 0.64;0.87) and a 41% reduction in hip fractures (RR 0.59 CI 0.42;0.83) (fig 4).

In a 3 year extension of the HORIZON study,\(^10\) 1233 patients were randomized to receive zoledronate for a further 3 years or to take placebo. Patients continuing with zoledronate had a significantly lower risk of morphometric vertebral fractures but there was no difference in the incidence of hip or non-vertebral fractures between the two groups. The authors concluded that given these findings, the majority of patients could stop zoledronate therapy after 3 years but that consideration should be given to continuing therapy in those patients who are at high risk for vertebral fracture.

**Ibandronate**

Ibandronate has recently become available for treatment of osteoporotic patients in South Africa. It is administered as a 3mg intravenous injection administered 3 monthly. The pivotal fracture study on ibandronate, the BONE study,\(^11\) used oral ibandronate as a 2.5mg daily oral dose or 20mg on alternate days for 12 doses every 3 months. In the group receiving 2.5mg daily there was a 62% reduction in vertebral fractures (RR 0.38 CI 0.34-0.74). There was no reduction in non-vertebral or hip fractures. In a post hoc analysis of patients with T-scores of \(\leq -3.0\) there was a significant reduction in non-vertebral
fractures. A meta-analysis of studies using higher dose forms of ibandronate including the 3mg three monthly infusion suggested that ibandronate in these higher dose forms is effective in reducing non-vertebral fractures. Not all of the studies were, however, placebo controlled and there was a limited amount of baseline data available for multivariate analysis. No studies on ibandronate have shown a reduction in hip fractures.

**Glucocorticoid induced osteoporosis**

Bisphosphonates have been shown to be effective agents in improving bone density and preventing vertebral fractures in patients receiving chronic glucocorticoids and bisphosphonates are considered first line agents for the treatment of glucocorticoid induced osteoporosis.

**Side effects of bisphosphonate therapy**

**Upper gastro-intestinal symptoms**

The most common side effect of oral bisphosphonates is upper gastro-intestinal symptoms such as dyspepsia. Patients with gastro-oesophageal reflux can potentially develop severe reflux oesophagitis. Oral bisphosphonates are therefore best avoided in patients with upper gastro-intestinal symptoms.

**Acute phase reaction**

The acute phase reaction consists of a collection of influenza like symptoms including pyrexia, myalgia, arthralgia and headache that occur in the first week following the administration of an intravenous bisphosphonate. In the HORIZON study 31.6% of patients developed any these symptoms after the first infusion. This reaction is much less common after the second infusion (6.6%) and the third infusion (2.8%). It is thought to be related to the inhibition of FPP synthase and increase of TNF-α. It has been seen to occur more commonly in patients who previously took oral bisphosphonates and in patients who are receiving non-steroidal anti-inflammatories. This reaction inevitably resolves spontaneously after a few days.

**Skin reactions**

Allergic skin reactions can occur but are rare.

**Acute renal failure**

This can occur with intravenous bisphosphonates if they are injected rapidly. It is important to ensure adequate hydration of patients prior to infusion of bisphosphonates. Bisphosphonates should not be used in patients with a creatinine clearance of < 35ml/minute.

**Osteonecrosis of the jaw (ONJ).**

This is a rare complication of bisphosphonate usage. It is defined as an area of exposed bone in the maxilla-facial region that does not heal within 8 weeks in a patient who is currently receiving osteoporosis medication and has not had radiation to the head and neck region. More than 80% of cases occur in patients with an underlying malignancy and 90% occur in patients receiving high dose intravenous bisphosphonates. It is extremely rare in patients being treated with bisphosphonates in doses used for osteoporosis (0.01-0.0004%). NOFSA has published guidelines addressing the issue of bisphosphonates and ONJ. These guidelines recommend that good oral hygiene and regular dental visits are advisable and that if major dental surgery is anticipated, it should be completed prior to starting bisphosphonate therapy. In subjects already receiving bisphosphonates dental surgery is not contra-indicated and there is no evidence suggesting the need for stopping bisphosphonates if implants are planned.

**Atypical Fragility Fractures (AFF)**

These are spontaneous non-spine fractures, predominantly in cortical bone rich areas such as subtrochanteric or diaphyseal femur. These fractures are more commonly associated with chronic long-term alendronate use. It is a rare phenomenon with an estimated incidence of 47/100,000 patient years after 2-5 years use of bisphosphonates and of 117/100,000 patient years after using bisphosphonates for 5-9 years. However, given the concerns about the possible adverse effect of long-term bisphosphonates on bone quality, and given the data as discussed above from the FLEX study on alendronate and the 3-6 year data from the HORIZON study extension which showed that the in majority of patients use of alendronate after 5 years and zoledronate after 3 years did not result in substantial fracture benefit, a review of the need for continuing treatment after those timeframes is appropriate. Should the patient be considered to remain at high risk for vertebral fracture ongoing treatment should be considered. This would include:

- Patients with femoral neck T-scores of ≤ -2.5.
- Patients with incident vertebral or femoral neck fractures whilst on therapy.
- Patients with multiple vertebral fractures at initiation of therapy.
- Patients >75 years.

In other patients a drug holiday should be considered with follow up of the patients by DXA and/or markers of bone resorption after a year.

**Conclusion**
The bisphosphonates remain effective and relatively safe agents for treating patients at high risk of fragility fractures. Careful patient selection and follow-up will keep both side-effects and long-term adverse events to a minimum.

References

% of people over the age of 65 will fall at least once, 15% will fall more often and the risk of falling increases with age. 5% of these falls will result in fractures. Fractures are not the only consequence of falling. Falling increases the fear of falling, which in turn, results in an increased risk of falls. Falls also lead to lack of confidence, reducing physical activity, social embarrassment, a significant loss of quality of life and even death. Falls even when not associated with a fracture, might result in an inability to get up and call for help in persons living on their own. This in turn could lead to hypothermia, dehydration and mortality.

As general practitioners, gynaecologists and other health care providers, we spend quite a lot of time considering bone densities and medical interventions to prevent fractures. It is however important to consider trying to reduce the risk of falling thus preventing the fractures and all the other problems related to falling in older people.

Hopefully the following information will help in assessing who is at risk of falling and giving advice to these people and their practitioners about avoiding falls and generally improving health.

**Fall risk assessment**

By looking at **Tables 1 and 2**, one can see that there are numerous factors which place people at risk of falling. Because there is such a wide range of risk factors, it is important to recognise that the risk of having a fall is probably multifactorial in origin. When taking a careful history and doing a thorough examination of older people, one should look for as many of these factors as possible in order to give appropriate advice concerning this problem.

It should also be noted in **Table 1** that the various risk factors might be associated with either disease or natural ageing.

As with all clinical interventions, the first step is a full medical history and examination. The history should also involve details from family members or care givers.

History of cardiac events, neurological symptoms and psychological status is a good starting point. Questions concerning dizziness and careful attention to a history of medications is vital (psychotropic drugs, sleeping pills, hypertensive medication, anti-histamines, anti-convulsants and anti depressants). Recreational drugs are uncommon in the elderly but alcohol plays a part in the risk of falling.

Ask questions about exercise and other activities. Both lack of exercise and increased exercise are risk factors of falling, the latter probably due to fit health elderly people partaking in exercises with an inherent risk of accidental falls.

History of previous falls and fear of falling are very good indicators of risk.

Urinary symptoms such as urge incontinence, urgency and nocturia also increase the risk of falls.

Physical examination should proceed as with any other medical consultation, paying special attention to blood pressure, including checking for postural hypotension which would be indicated by a drop in pressure of more than 20mmHg when standing, compared with sitting or lying. Carotid sinus hypersensitivity should also be checked.

Observation of gait and assessment of neurological disorders and obvious weakness can be done in the normal clinical environment.

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**Table 1 - Physical and medical risks**

- Weakness
- Gait disorders
- History of falling >2 in a year
- Fear of falling
- Visual defects, hearing loss
- Cognitive impairment and dementia
- Urinary problems (incontinence, urgency, nocturia)
- Medication
- Dizziness (drugs, hypotension, arrhythmias)
- Poor nutritional status
- Pain
- Alcohol
- Exercise related

**Table 2 - Extrinsic risk factors**

- Loose carpets
- Slippery floors
- Unmarked stairways
- Lack of supporting rails
- Poorly placed furnishings
- Inappropriate footwear
- Institutional living
Tools for risk assessment

A number of tools for risk assessment have been developed. These include measurement of physical functioning, strength and physical activity scores (Table 3).

### Table 3 - Tests of physical functioning

<table>
<thead>
<tr>
<th>1. Timed Up and Go Test</th>
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<tr>
<td>2. Simple Sit To Stand Test With 5 Repeats</td>
</tr>
<tr>
<td>3. Alternate Step Tests</td>
</tr>
<tr>
<td>4. Six Minute Walk Test</td>
</tr>
</tbody>
</table>

All scoring systems make the point that falling is of multi-factorial origin and that care should be taken to pay attention to all factors rather than just one or two.

The Timed Up and Go Test is a validated and simple test to perform to assess function. The patient is requested to stand up from a 48cm chair, walk 3m, turn around through 180 degrees and walk back to the chair and be re-seated. 15sec is recommended as the time required to perform this test in an adequately functioning person.4

Other tests include tests for functional limitations assessed by questionnaires concerning the degree of difficulty with climbing stairs, walking 5 minutes, rising from sitting, dressing and undressing, using private and public transport and the ability to cut one’s own toenails.

Grip strength tests have also been used as well as scores of physical activity (LASA Physical Activity Questionnaire). Stel et al 2003 divided an interesting “classification tree” for predicting recurrent falls. This paper makes interesting reading, showing the multi-factorial nature of falls and grouping of some risk factors.5

The Mini Mental Test is a validated short form questionnaire which assesses cognitive function, dementia and risk of Alzheimer’s disease. This can be used to assess the patient’s cognitive function.6

Interventions to prevent falls

Because of the multi-factorial nature of risk of falling, strong evidence based information regarding interventions is sometimes difficult to assess. There are, however, a number of interventions that have stood up to scientific investigation.

A Cochrane report found that multiple component group exercise and multiple component home based exercise reduced the risk of falling and the risk of fall related fractures. Tai Chi, a popular exercise in the East amongst the elderly also reduced the risk of falling.7 This report also found that home safety interventions reduced the risk of falling.

Interestingly, this review showed conflicting evidence when attention was paid to improving visual defects. There was in fact an increase in falls, particularly outdoors in people who usually partook in only a little outdoor activity. Changing from multi-focal spectacles to single lense spectacles reduced the risk of falling in both indoor and outdoor activities.

The same review showed that gradual withdrawal of psychotropic medication, multi-focal podiatry, including foot and ankle exercises in people with foot pain, all reduced the risks of falls.

Other studies have confirmed the benefit of withdrawing or changing medication such as psychotropic drugs.8

Supplementation with vitamin D seems to benefit those who are deficient at the start of the investigations and one study suggested that vitamin D supplementation of 700-1000 u/day reduced the risk of falling by 20%.9

The prevention of falls in the elderly trial (PROFET) looked at two interventions.

1. Medical interventions having identified risk factors.
2. Occupational therapy assessment.

They found that the intervention group had less falls than the control group, but this was based on relatively small numbers. Patients in the intervention group were more likely to be able to go out alone, the risk of serious injury was not significantly different in the two groups.10

NICE guidelines of 2004 and updated in 2013 recommend multi-factorial assessment, followed by multi-factorial interventions including strength and balance training, home hazard assessment and interventions, visual assessment and medication review.11

More technical interventions such as cardiac pacemakers are beneficial in patients who have carotid node hypersensitivity.

Conclusion

Falling in the elderly carries serious consequences for both serious injury, reduction in quality of life and mortality.
Risk assessment for falls can be relatively simple and is well within the skills of primary health care providers.

Risk assessment and interventions all benefit from the inclusion of physiotherapist and occupational therapists. All medical healthcare providers should be made aware of the risks, assessment and interventions available around falling in the elderly during their training.

References

7. Lesley D Gillespie, M Clare Robertson, William Gillespie et al. Interventions for preventing falls in older people living in the community (Cochrane review).
**SAMS NEWS by fax - Introduction**

Members of the South African Menopause Society obtain regular one page concise summaries on various topics by fax. Some readers of Menopause Focus are not members of SAMS and might be interested to see examples of some of these reviews. Membership of SAMS would allow you to receive these very useful summaries of clinical issues.

**SAMS NEWS by fax - May 2014**

**Combined hormone therapy for high risk patients**

Dr Alice Shaw B MED Sc, MD (CAN), FCOG(SA)
Gynaecologist and Obstetrician, Knysna Life Hospital (on behalf of the SAMS council)

It has been suggested that instead of depriving symptomatic high risk patients of hormone therapy, choosing the best therapy for these patients may enable us to avoid possible complications. Transdermal oestrogen 50 ug or less combined with micronized progesterone has been proposed as the best combination.

Four safety concerns identified by the WHI study and hormone therapy were VTE, myocardial infarction, stroke and breast cancer.

**Venous thrombosis**

Oral oestrogen is known to increase the risk of VTE and combined therapy even more so. Transdermal oestrogen does not influence the coagulation cascade. It does not increase the risk of thromboembolism even in patients with risk factors e.g. obesity, thrombophilia or personal history of VTE. The type of progesterone/progestin used has shown to influence risk. In both the ESTHER case control study and the E3N study micronized progesterone and pregnane progestogens did not increase risk whereas pregnane progestogens did.

**Myocardial infarction**

It is well known that oestrogen has a preventative role in atherosclerosis if initiated early. Oestrogens induce the synthesis of nitric oxide, a potent vasodilator. Transdermal oestrogens do not increase inflammatory markers associated with atherosclerosis. Androgenic progestogens such as MPA and NETA partially negate these beneficial effects while micronized progesterone and non-androgenic progestogens do not.

Diabetes is a major risk factor for myocardial infarction. Oestrogen therapy decreases the incidence of new onset diabetes in menopausal women. The addition of micronized progesterone, cyloproterone acetate or NETA did not adversely affect this finding.

**Stroke**

Oral oestrogens do increase the risk of stroke but as the incidence of stroke is low in younger women this is probably not of clinical significance in healthy women. In a case control study matched controls from women 50 - 79 years transdermal oestrogens 50ug or lower did not increase risk whereas low and high dose oral oestrogen did. Hypertension is a major risk factor. Conjugated oestrogens may increase blood pressure. Micronized progesterone tends to reduce blood pressure.

**Breast cancer**

Combined hormone therapy is associated with an increased risk of breast cancer while oestrogen alone appears to be protective. Progestogens are not a uniform class and can inhibit or stimulate the proliferation of breast cancer cells. MPA enhances breast cell proliferation in combination with oestrogen and this may be related to its glucocorticoid activity. Micronized progesterone is not associated with increased breast density. In the French E3N cohort study micronized progesterone did not increase breast cancer risk whereas oestrogen and synthetic progestins except dydrogesterone did.

**Conclusion**

Observational data strongly suggests that transdermal oestrogen and micronized progesterone is a safe hormone therapy to use in high risk women. As most guidelines are suggesting that hormone therapy can be extended in older women this approach will become more important.

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1. Mueck AO Postmenopausal hormone replacement therapy and cardiovascular disease: the value of transdermal estradiol and micronized progesterone Climacteric 2012;15(Suppl. 1):11-17
2. L'Hermite M HRT optimization, using transdermal estradiol plus micronized progesterone, a safer HRT
Vaginal lubricants in the menopause

Dr Carol Thomas MBChB(UCT), FCOG(SA), MMed(O&G)(UCT)
Specialist Gynaecologist and Director of the WomanSpace and iMobiMaMa (on behalf of the SAMS council)

Although the evidence for improving urogenital and, particularly, vaginal epithelium integrity with local oestrogen preparations in cream, pessary or slow-release vaginal ring form, is undisputed and forms part of our daily prescribing habits, the beneficial effect on vaginal health occurs over time and may not address the immediate needs of the woman sitting in your office. Discontinuation of local oestrogen preparation and disappointment with our care may follow, especially as vaginal dryness and the effect of urogenital ageing may be issues that the woman may only volunteer at the end of a consultation or on a subsequent occasion when she has developed a sufficiently trusting relationship with you. Often, her quality of life and/or her relationship may be significantly compromised by the time of presentation. Many women are also not aware that they do not need a prescription for some topical oestrogen products that may be requested over the counter.

What they may encounter is an array of personal lubricants with a dazzling array of trade names (e.g. Probe®, Sylk®, Astroglide®) widely available on pharmacy, adult sex shop, supermarket and online shelves. Personal lubricants are not regulated and, therefore, make composition and quality difficult to assess, but they fall broadly into 2 categories: water or silicone based.

Glycerine water-based lubricants, like K-Y Jelly®, are well-known and ubiquitous, but need to be re-applied often because viscosity changes during use. These have often been used by the woman before she asks her question about which lubricants you would suggest.

Silicone-based lubricants are more expensive, but the amount required is less and repeated applications may not be as necessary as with water-based lubricants. They are not recommended for use with latex condoms because of concerns re slippage and breakage.

Alessandro Genazzi reviewed 9 published RCT’s on the non-hormonal bioadhesive polycarbophil vaginal moisturiser (Replens®) and conducted a well-powered study which concluded that it was an effective treatment for vaginal atrophy in women on and off hormonal therapy as evidenced by increased vaginal elasticity, hydration of the vaginal epithelium, patient acceptance and significant drop in vaginal pH. Cost is a factor and 12 to 24 weeks of treatment may be necessary initially.

A total of 2,453 women aged between 18 and 68 completed a 5-week internet-based, double-blind prospective daily diary study by Debra Herbenick, et al and were assigned to use one of six water- or silicone-based lubricants. Daily diary data included reports of penile–vaginal sex, penile–anal sex, solo sex, lubricant use, lubricant application, ratings of sexual pleasure and satisfaction, and genital symptoms (tearing, discomfort, entry pain, penetration pain, after penetration pain, burning, itching and bleeding). Water-based lubricants were associated with fewer genital symptoms compared with silicone-based lubricants. In addition, the use of a water-based or silicone-based lubricant was associated with higher ratings of sexual pleasure and satisfaction for solo sex and penile–vaginal sex.

The pre-enrolment figure of 60% ever lubricant use in the previous month gives some indication of the extent of lubrication use and may provide a window on how under reported the issue around lubrication and sexual pleasure may be!

As clinicians we may have to initiate the discussion around concomitant or initial lubricant use when dealing with the issues around urogenital ageing and atrophy. We also need to be aware of which products are available for our patients to use. A phone call to the local pharmacy and a walk down the supermarket aisle may be just what the doctor ordered. In addition to, or when local oestrogen is contra-indicated, personal lubricants and vaginal moisturisers are to be encouraged in menopausal women when vaginal integrity has been compromised.

References
The statin wars

Professor Athol Kent MBChB, MPhil, FRCOG
Associate Professor, Department of Obstetrics & Gynaecology, University of Cape Town

There is a major debate taking place in the UK about statins being offered to people at moderate risk of cardiovascular disease (CVD). The response below is the author’s opinion about the Believers and the Doubters on the topic.

Why does the controversy over statins concern obstetricians and gynaecologists in the UK and worldwide especially those dealing with mature women?

Firstly, the proposed national campaign in the UK to place large numbers of its citizens on statins represents a sea change in the way in which medicine might be practiced in future. It is a fundamental move from doctors treating sick people who consult them, to the NHS asking healthy people to see their doctors about evaluating their cardiovascular disease risk and possibly ameliorating such risk with drugs.

It heralds the arrival of “mass medicine”.

Secondly, we need to formulate our own ideas about “medicalisation by biochemistry”. Most people in the moderate zone of CVD risk could lower their chances by lifestyle modification if suitably motivated. Does offering a drug instead represent a sensible option or a cop-out? Is this good preventative medicine or the thin edge of the over-medicalisation wedge?

Thirdly, if the campaign proves successful we will see many more patients on statins which we will need to take into account when evaluating symptoms or prescribing medication. It will be up to us to endorse or gainsay national guidelines – never mind considering whether we should be evaluated for statins ourselves.

Fourthly, outside of a National Health Service – or even within it, does this major expenditure make financial and quality-of-life sense to the individual and the population at large? At the end of the day are the savings of life and morbidity going to be worth the time, energy, effort and expense?

Finally, is the proof good enough? Statins are useful in reducing CVD events in high-risk patients but will they protect moderate-risk patients who are not sufficiently motivated to change their lifestyles but are sufficiently motivated to take statins in the long-term? No pilot trials have been published to show the benefits exceed the harms in this group of people in a “real world” situation.

THE BELIEVERS

Those in favour of lowering the threshold for statin introduction are spear-headed by one of the most influential bodies in world medicine. They have thrown down the gauntlet and their arguments deserve thoughtful reflection.

The UK National Institute for Health and Care Excellence (NICE) seems in no doubt that it is in the public interest to widen the use of statins to reduce mortality and morbidity from CVD in that country. A 300 page guideline extols the virtues of citizens consulting with their GPs and “lowering their risk” through statins (Rabar et al BMJ 2014;349:g4356).

The consultation is nothing if not thorough. The information to be communicated is considerable: starting with advice about lifestyle modification and a follow-up interview. Blood tests should precede prescription including total cholesterol, non-HDL cholesterol, HDL cholesterol and triglycerides, glycated haemoglobin, renal function and estimated glomerular filtration rate, transaminases and thyroid stimulating hormonal levels. Discussions are to include the possible side-effects, type of statin, dosages, monitoring, follow-up prescription and dispensing.

These scientists believe that people with a 10% chance of developing cardiovascular disease over the next 10 years should take statins. They calculate that if 1000 such people took statins for 3 years then there would be 2 lives saved, 4 strokes and 7 infarcts prevented. In numbers needed to treat, 77 people would have to take statins for 3 years to avoid one CVD event in this moderate risk group.

If the campaign is successful there will be a major reduction in CVD which will result in lower morbidity and mortality with large savings in acute and chronic CVD costs.

THE DOUBTERS

General practitioners (GPs)

GPs will be asked to invite everyone in their practice between 30 and 85 years to attend a consultation. They will have to be au fait with NICE guidelines and be in agreement with their conclusions.
They will try to convince those in the “10% in 10 years” bracket to change their lifestyle (which we know is unlikely) and run blood tests. A second visit, results discussion and side effects warnings will end with a prescription. All being well this will result in an estimated 4.5 million Britons being treated with statins – all by GPs who are already overworked, dealing with 40 million more consultations than 5 years ago (Wilkinson Lancet 2014;384:295-6). Even a straw poll in the BMJ (16th August 2014) indicated that the majority (63%) of readers thought GPs should not prescribe statins for primary prevention of CVD.

Patients

If invited, will Pat Public respond? Will she or he present for a minimum of two consultations, submit to blood tests, fail to heed the lifestyle advice, fill their prescriptions and take statins in the long-term?

They will need to be motivated for the greater good of the population and believe in “group altruism”. They will have to believe in the odds, which are not proven by RCTs, when we know that people in complex situations decide emotionally using “affect heuristics” rather than rational processes (Dobelli: The art of thinking clearly. 2013 pp 202-4. Sceptre).

Will it be the well motivated who present for this arduous screening programme or the poorly motivated? Too often it is the poorly inspired who would most benefit from the intervention for example in cervical cytology screening and HPV vaccinations. Will the call to statins be different?

Side effects

All drugs have side effects and although those associated with statins have recently been over-rated, they still exist. Placing millions of healthy people on drugs requires a clear “benefits over harms” ratio – derived from rigorous trials with precise outcomes in the target population over the long-term. These have not been published; only statistical risks.

For the proposed programme to be scientifically monitored, all side effects will have to be evaluated as real or not, attributable or not, and submitted to a central resource centre for assessment. Without such detail this is a risky experiment and ethically suspect (Goldacre & Smeeth BMJ 2014;349:g4745).

Costs

The statin campaign is being mooted in the UK and will have to be accepted by those in charge of NHS expenditure.

The money spent on GP consultations, patients’ time, blood tests, prescribing and dispensing, side effect monitoring and running the programme will cost millions of pounds. Will these be balanced by quality-adjusted life years plus reduced acute and chronic CVD costs and lives saved?

There is a hidden cost in asking healthy people to consider medication. Each person agreeing to take the medication will have to be conscientious and be aware of any symptoms that may arise on the statins. This may be a life-long commitment and if they fail to comply or stop because of side effects and then develop CVD there may be regrets, remorse or feelings of being let down by the system or themselves. And what if they develop CVD on the statins? Can they sue the NHS?

Actuarial analyses look very different when things go wrong.

Much is made of the low costs of statins but no drug company is going to sell their products at cost, generics or not. Can you imagine the celebrations in pharmaceutical board rooms if “mass medicine” arrives courtesy of a scientific “coterie”?

The author is a doubter both scientifically and pragmatically.
Dear all

It is indeed with regret that I write my final newsletter as the President of the South African Menopause Society. It has been a privilege and honour to have been given the opportunity to contribute to women’s health after the menopause in Southern Africa.

Women will live a substantial portion of their life after the menopause and it is therefore imperative that we continue to make it a priority at improving their quality of life.

Longevity is assured in the developed countries, and even despite the ravages of HIV, HPV and tuberculosis in Africa, life span of our women in Southern Africa is improving with every decade. Retirement age in Europe has now been increased to 68 years of age, whilst many countries in Asia, including China, are considering 70 years of age to be retirement age.

The postmenopausal woman continues to contribute substantially beyond her menopause, a fact clearly reflected in Time Magazine’s most influential women of the last century, interestingly many of which continued to be forceful figures in their 70’s and even their 80’s.

Never have more women been liberated, educated and found lasting and meaningful careers which contribute significantly to global leadership, economic development and much needed resources than today. I sense that if Southern Africa did not have such a deplorable unemployment rate among the youth, women beyond menopause would be encouraged to contribute for many more years beyond the menopause in all walks of life.

I wish to thank all the SAMS council members for their support, encouragement and advice during the last two years. I thank Ann Lake and her team for the much appreciated commitment to Menopause Focus and to Alison Shaw for always being in the background and for offering of her time so willingly. To all I am very grateful.

I have no doubt that SAMS will continue surging ahead under the leadership of Peter Roos, and I wish him all the best for his coming term as the new president of SAMS. SAMS has over the last 20 years tried to make a difference in South Africa and I have no doubt that it will continue to do so.

Kind regards to all readers of Menopause Focus and to all SAMS members. I urge you all to continue your interest and attempts at improving women’s health and well being.

I hope that all the delegates who attend the SAMS congress find it meaningful, informative and most enjoyable.

Franco Guidozzi

On behalf of the editorial board and the readers of Menopause Focus, Ann Lake Publications would like to extend our sincere thanks to Professor Franco Guidozzi for his expert guidance of and contribution to Menopause Focus during his tenure as editor. His passion and dedication has contributed significantly to the success of Menopause Focus.
Treating disorders of uterine bleeding

Non-androgenic<sup>1</sup>
Non-sedating<sup>2</sup>

Dydrogesterone e.g. Duphaston<sup>®</sup> provides relief from multiple symptoms<sup>3</sup>
