Summary
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This thesis was designed to evaluate the effect of hormone therapy (HT) and specifically tibolone on sexual function in postmenopausal women with female sexual dysfunction (FSD).

To be able to answer this general question several considerations were explored before having identified the right angle to perform this project: therefore several sub-research questions were defined:

1. What is the attitude of postmenopausal women and doctors regarding sexuality after menopause?
2. What is the correct research approach in investigating pharmacological intervention for FSD?
3. What is the effect of tibolone, combined oestrogen plus progestagen and raloxifene (a selective oestrogen receptor modulator) on sexual function in postmenopausal women?
4. What is the net androgenic effect of tibolone over and above its oestrogenic effects in postmenopausal women with FSD?

The aim of our study was to contribute to the current knowledge about the role of hormone therapy on female sexual function and to search for pharmacological treatment options which could fit in a multi-dimensional, but also clinically practical approach in the treatment of sexual problems.

Chapter 4
Sexual Well-Being after 50: A European Survey among Women and Physicians

The objective of this study was to describe current women's thoughts about sexuality after menopause in various European countries and to identify current physicians attitudes towards sexuality during and after menopause.

A survey was conducted in 6 European countries interviewing over 3000 menopausal women and 600 doctors who treated menopausal women. The majority of women (67%) reported to experience symptoms affecting sexual well-being including vaginal pain/dryness and/or a reduced sexual interest and desire which negatively influenced their quality of life and the relationship with their partner. To them, the main reason for a reduced sex-life was menopause and growing older. In spite of a high prevalence of sexual problems, many women remained sexually active but experienced less pleasure from sex.

To 61% of the women, sexual activity remained as important as before the menopause and a similar percentage reported that they would enjoy their life more if their sex drive would improve to previous levels. In spite of experiencing a reduced sexual interest and/or desire, the majority of women was satisfied with their sexual relationship.
Vaginal dryness/dyspareunia was not reported as a major factor influencing quality of life or sexuality. Most women with sexual problems had never considered a treatment, as they were not bothered enough by their sexual problem. 35% would consider to take a drug to help solving sexual problems, if this was available. Women felt they were more likely to discuss their sexual problem if the doctor would bring up the subject.

Physicians underestimated the prevalence of a reduced sexual desire and interest in their patients, however, they overestimated the prevalence of vaginal dryness and dyspareunia as a reason for postmenopausal sexual problems. More than one third of the doctors were the opinion that discussing sexual problems is a taboo and also one third reported to find it difficult to discuss sexual health concerns with elderly patients. Apparently, women and doctors see menopause related sexual problems differently: educating both women and doctors concerning sexuality may remain one of the crucial elements to resolve menopause related sexual problems prior to starting any treatment.

Chapter 5

This chapter addresses the study of FSD as this is an evolving research area in which a correct research approach has not been fully established due the fact that a new female sexual response model has recently been proposed followed by continuous revisions of the definition of FSD.

The aim of this study was to evaluate the needs in research into intervention in female sexual dysfunction (FSD) by reviewing published randomized controlled pharmaceutical intervention studies. This chapter summarizes the limitations and issues of these studies and the relevance of the outcomes for clinical practice. Unresolved questions were identified and proposals to optimize the design of future studies made.

The main outcome of our review was that a standard methodology for research in this field is lacking especially regarding the population inclusion requirements and tools for the measurement of change in sexual functioning.

In order to be able to measure a treatment effect of the intervention which is clinically meaningful for a woman the following issues need to be resolved prior to initiating new intervention trials in FSD: A universally accepted method for defining the FSD population is needed and as a result a consensus should be reached for appropriate inclusion and exclusion criteria for FSD trials. Similarly main outcome measures appropriate for the evaluation of drug intervention should be defined. Trial endpoints need to reflect clinically relevant outcomes and should be embedded in a bio-psycho-social sexual response model for women.
Chapter 6

Effects of tibolone and raloxifene on health related quality of life and sexual function

This chapter compares the effects of tibolone and raloxifene on health related quality of life, sexuality and vaginal atrophy in elderly, osteopenic but otherwise healthy, postmenopausal women. We performed a two years, prospective, double blind clinical trial in 308 women (mean age 66 years) who were randomized to tibolone or raloxifene.

Health related quality of life was assessed by the Women’s Health Questionnaire (WHQ), sexual function by the McCoy Female Sexuality Questionnaire (MFSQ) and vaginal atrophy by assessing the Karyopycnotic Index (KI) and Vaginal Maturation (VM).

Tibolone improved health-related quality of life, with WHQ values approximating those for premenopausal women, whilst women treated with raloxifene showed a trend towards a poorer quality of life. Changes from baseline of a few WHQ domains were significantly larger in favor of the tibolone group when compared to the raloxifene group, particularly the sexual behavior, attractiveness and vasomotor symptoms domains all showed a statistically significant improvement from baseline.

Less than half of the women in the trial provided data for the MFSQ, the main reason being the absence of sexual activity. No difference could be assessed between the tibolone and raloxifene group in mean total score and separate domains scores of the MFSQ, except for the vaginal lubrication domain (p= 0.037). This was also reflected in the VM and KI index which showed an improvement with tibolone, whilst there were no meaningful changes in the raloxifene group.

A post-hoc separate item analysis showed significant differences in favor of the tibolone treated women on a few questions at various time points which included the presence of sexual thoughts and fantasies (p=0.047), feeling aroused/excited (p=0.038) and a decrease in pain during intercourse (p=0.02).

Tibolone and raloxifene were equally well tolerated and no serious adverse events regarding the cerebrovascular and/or cardiovascular system were reported.

This study shows that also in older postmenopausal women, tibolone treatment showed a trend towards an improvement in quality of life and sexuality whereas raloxifene has no added benefits on these aspects.

Chapter 7

Effects of tibolone versus low dose oral E2/NETA on urogenital complaints, sexuality and quality of life in postmenopausal women: results of a randomized controlled clinical trial

This chapter addresses the effects of tibolone versus oral low dose E2/NETA (1mg/0.5mg) on sexual function, urogenital complaints and quality of life in postmenopausal women. We performed a 48-week multicenter, randomized, double blind, double dummy, group comparative trial. Several questionnaires were used to measure response to therapy:
the McCoy sexuality questionnaire for sexual function, the Women’s Health Questionnaire (WHQ) for health related quality of life and the Urogenital Complaints Scale (LUGCS). 572 postmenopausal women aged 45-65 years were included in this trial. After 48 weeks of treatment, both treatments showed an added benefit to healthy postmenopausal women by improving sexual function, quality of life and urogenital complaints when compared to baseline. Tibolone’s beneficial effect on sexual function was, however, more pronounced and particularly present in a subset of women who were identified with sexual problems at baseline. A significantly greater effect of tibolone on the increase in the mean total score of the McCoy sexuality questionnaire (p=0.038 for the total trial population) and the mean score of the McCoy sexual interest domain was shown. In addition, the “satisfaction with the sexual relationship”- domain of the WHQ showed a clinically relevant improvement in the tibolone treated women and not in the E₂/NETA treated women.

Chapter 8
Tibolone and transdermal E₂/NETA for the treatment of Female Sexual Dysfunction in naturally menopausal women: results of a randomized active-controlled trial

This chapter focuses on the effects of tibolone in sexual function over and above its documented ability to relieve climacteric symptoms in postmenopausal women with FSD. In order to make a scientifically justified comparison, we performed a 24 week, randomized, double blind clinical trial with tibolone versus transdermal E₂/NETA as an active comparator. The primary objective was to assess differences between treatment groups in the change from baseline for the composite sub-score of the arousal, desire and satisfaction domains of the self-reported FSFI (Female Sexual Function Index). Secondary outcomes included the outcomes of the Female Sexual Distress Scale (FSDS) and the frequency of satisfying sexual events (daily diaries).

403 women, mean age 56 were included. In the per-protocol analysis, which consisted out of the women who had been compliant to the trial medication and had a sexual partner who stayed sexually functional during the trial, the increase in FSFI scores was significantly larger in the tibolone group when compared with the E₂/NETA patch group at week 24 (p=0.036 and p=0.025 for the composite sub-score and total FSFI score respectively). This difference could not be assessed in the intent-to-treat analysis. At week 24, the satisfying sexual event rate increased from 3 to 4 times per 28 days (p<0.001 from baseline for both groups), with no difference between groups. The FSDS showed a significant decrease from baseline (p<0.001) which was comparable for both treatment groups. Of importance, a significant reduction in refusal of the “initiative for sexual activity” of the partner was seen in favour of tibolone-treated women when compared with E₂/NETA-treated women (-45% vs. -28%; p<0.001). Tibolone was associated with a significant reduction in mean SHBG levels (p=0.001) and an increase in free T levels (p<0.001); both of these effects were significantly different from those of E₂/NETA. However, no correlation between hormone levels and outcomes regarding sexual
unction could be assessed. The overall incidence of adverse events was generally low and comparable between groups, although a substantially higher percentage of women in the E₂/NETA group discontinued the trial due to irregular vaginal bleeding.

In conclusion, although both treatments resulted in a significant improvement in sexuality scores of the FSFI, a significant reduction in female sexual distress and a greater frequency of satisfying sexual events when compared to baseline, tibolone is more likely to restore sexual function than transdermal E+P and has a better tolerability profile.

Chapter 9
Tolerability aspects of tibolone versus transdermal E₂/NETA treatment in postmenopausal women with FSD: results of a randomized controlled trial

This chapter addresses tolerability aspects of tibolone and transdermal E₂/NETA (50 μg/140μg) with the main outcome measure being the vaginal bleeding event rate. As a part of the randomized, double blind clinical trial with tibolone versus transdermal E₂/NETA, a primary safety objective was included which specifically determined the tolerability profile on the reproductive system in each of the two treatment groups. Bleeding/spotting events were recorded in a daily diary that was distributed at screening and collected at each follow up visit. The bleeding/spotting rates were determined as the percentage of women experiencing at least one bleeding/spotting event per 12-week period (i.e. weeks 1-12 and weeks 13-24). Women were included in the period analysis provided they had received treatment for the entire 84 days and had no more than 10 days of missing values. In both periods, women on tibolone experienced significantly less bleeding/spotting compared with transdermal E₂/NETA. During weeks 1-12, the bleeding/spotting incidence was 16% vs. 56% (p<0.001) for tibolone and E₂/NETA, respectively, and during weeks 13-24, 12% vs. 51% (p<0.001) for tibolone and E₂/NETA, respectively. At the end of the study, 24% of women given tibolone had experienced at least one bleeding/spotting day compared with 72% of those given E₂/NETA (p<0.001).

The overall incidence of breast signs and symptoms was significantly greater in the E₂/NETA group than in the tibolone group (11% vs. 4%; p=0.015). Adverse events besides those affecting the reproductive system were generally low and comparable between treatment groups.

In conclusion, tibolone has a significantly better tolerability profile than transdermal E₂/NETA as measured by the incidence of vaginal bleeding and breast pain, and is associated with a better treatment continuation.

Chapter 10
Pharmacotherapy intervention for Female Sexual Dysfunction: explorative analyses of a randomized controlled trial

This chapter evaluates into more detail the outcome measures of the studies presented in the previous two chapters, since these kind of trials are particularly susceptible to
bias by their nature (human behaviour and pharmacological intervention). The aim of the present study was to gain insight as to which potential confounders may have influenced the LISA study results and how to interpret the data.

Data were obtained from the FSFI, the FSDS and the Women's Health Questionnaire (WHQ) and analyses concerning the screening and baseline data set were performed on all women screened and all women randomized respectively. Analyses concerning the post-baseline data were performed on the ITT group, using the last observation carried forward approach.

The outcomes of our explorative analyses were the following:

The study population was well defined and reflected a true FSD population. A small but significant placebo effect was seen during the run-in phase of the trial (p<0.001) and might have ruled out a significant placebo effect during the active treatment part of the trial. Systematic differences between mean total scores of the FSFI questionnaire between continents exist (p=0.003). The consistency of the treatment effect was moderate to good at week 24 (Somer’s D coefficient 0.50). The FSDS and FSFI baseline scores are significantly influenced by a few factors such as age and years since menopause, the greatest factor being the country of origin.

Nevertheless, the initial conclusion that tibolone consistently improves sexual function over and above its ability to improve climacteric symptoms when compared to transdermal E2/NETA in women identified with FSD, was maintained.

Chapter 11

General discussion

European middle aged women experience menopause as a process that brings sexual changes able to impair their personal life. However, cultural values and health beliefs influence the perception of sexual changes and the need for treatment. One third of the women would be open for pharmacotherapy to help solving sexual problems if this was available. Counselling and education remains one of the pivotal pillars in a multi-dimensional treatment approach. The (indirect) effect on sexual function of restoring oestrogen levels by hormone treatment, especially transdermal estrogen plus progestagen formulations, is considerable, although elderly postmenopausal women might benefit less.

If pharmacotherapy is indicated, tibolone should be considered the first line therapy option for postmenopausal women with sexual problems/sexual dysfunction as both its direct effects on sexual function as well as its combined tolerability and safety profile is sufficiently established.