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Hormone Relacement Therapy

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ABSTRACT

More than 40 million women in the United States are now going through or are past menopause. Another 3.5 million or more will reach midlife in the next decade. As their life expectancy increases (mean life expectancy of women is now approximately 84 years), so does the need for therapeutic regimens related to reproductive function and aging in woman. Few medical treatments available to menopausal and postmenopausal women have as much potential benefit as well as possible health risks as hormone replacement therapy (HRT). Despite the increasing amount of scientific data available regarding the benefits of HRT, a degree of uncertainty still remains, both in the minds of some women, and with some health professionals, regarding the risks associated with long-term therapy. Even though the literature is voluminous, contradictory, and unclear, health providers must be able to keep abreast of current knowledge about the benefits, risks, and unknowns of these drugs. The purpose of this article is to provide a review and an update on the types of hormones available for HRT, their pharmacology and pharmacokinetics, and their risks, benefits, and contraindications. Newer products, specially compounded formulas, new regimens, and new modes of delivery that offer women alternatives and allow care to be individualized are described. In addition, some of the ongoing management dilemmas that practitioners face with the woman who chooses HRT are presented with practical solutions and suggestions.

INTRODUCTION:

[1,2]Hormone replacement therapy (HRT), also known as menopausal hormone therapy or postmenopausal hormone therapy, is a form of hormone therapy used to treat symptoms associated with female menopause . These symptoms can include hot flashes, vaginal atrophy, accelerated skin aging, vaginal dryness, decreased muscle mass, sexual dysfunction, and bone loss. They are in large part related to the diminished levels of sex hormones that occur during menopause.

[2]The main hormonal medications used in HRT for menopausal symptoms are estrogens and progestogens, amongst which progesterone is the major naturally-occurring female sex hormone and also a manufactured medication used in menopausal hormone therapy.[3,4]Though both classes of hormones can have symptomatic benefit, progestogen is specifically added to estrogen regimens when the uterus is present to avoid the increased risk of endometrial cancer. This is because unopposed estrogen therapy promotes endometrial thickening and can increase the risk of cancer, while progestogen reduces this risk. [5]Androgens like testosterone are sometimes used as well.[5] HRT is available through a variety of different routes.

[6]The long-term effects of HRT on most organ systems vary by age and time since the last physiological exposure to hormones, and there can be large differences in individual regimens, factors which have made analyzing effects difficult. [7,8]The Women's Health Initiative (WHI) is an ongoing study of over 27,000 women that began in 1991, with the most recent analyses suggesting that, when initiated within 10 years of menopause, HRT reduces all-cause mortality and risks of coronary disease, osteoporosis, and dementia; after 10 years the beneficial effects on mortality and coronary heart disease are no longer apparent, though there are decreased risks of hip and vertebral fractures and an increased risk of venous thromboembolism when taken orally.

[9]"Bioidentical" hormone replacement is a development in the 21st century and uses manufactured compounds with "exactly the same chemical and molecular structure as hormones that are produced in the human body."[10]These are mainly steroids derived from plants[11]and can be a component of either registered pharmaceutical or

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custom-made compounded preparations, with the latter generally not recommended by regulatory bodies due to their lack of standardization and formal oversight.[12]Bioidentical hormone replacement has inadequate clinical research to determine its safety and efficacy as of 2017.

[13]The current indications for use from the United States Food and Drug Administration (FDA) include short-term treatment of menopausal symptoms, such as vasomotor hot flashes or vaginal atrophy, and prevention of osteoporosis.

HISTORY AND DEVELOPMENT

[14]Menopausal symptoms can be grim, and the desire to replace the hormonal "deficit" with exogenous hormones remains strong. Since the 1950s, hormone replacement therapy has been used increasingly, [15]while evidence on the risks of unwanted side effects has accumulated. Twentyfiveyears ago, the increased risk of endometrial cancer emerged, resulting in the addition of progestogen. Cohort studies had examined estrogen alone and indicated important benefits, but, since the 1980s, combined preparations have dominated. Interpretations of the evidence were therefore confused, since whatever effects estrogen or progestogen have on disease will differ. Eventually, evidence of increased risk of combined therapy on breast cancer, coronary heart disease, stroke, and venous thromboembolism from a randomised trial was reported.[16]This trial was stopped early, after an average of five years' follow up among 17000 women, during which around 40% stopped their trial drugs. The results from the estrogen alone arm of the woman's health initiative study will reassess the role of combined therapy in 2005.

Because it may double the risk of breast cancer for long term use [17]and of heart disease in the first year of use, combined therapy is problematic. These risks are incommensurate with debilitating symptoms, but women need to be able to judge the risks for themselves. The balance now seems clearer than it was before we knew these risks; hormone replacement therapy works for symptoms but not for future health, which is not what had been widely promised.

[18]What have we learned over these decades? Firstly, current biological theory does not predict the effects of hormones on cancer and cardiovascular disease well. Secondly, mass prescription requires large randomized clinical trials with long follow ups. Observational studies of the putative effect of drugs, for coronary disease especially,[19]are unreliable. Thirdly, mass markets engender massive vested interests—personal, departmental, and corporate. Genuine care for women demands scientific independence, since uncertainty allows expert, but illegitimate, conviction too easily.Beware of all such profitable bandwagons.

[20]Understanding the pathogenesis of coronary heart disease, knowing that combined hormone replacement therapy has an unambiguously beneficial effect on lipid concentrations but increases the risk of coronary heart disease, is challenging if estrogen alone is cardioprotective. [21]Menopausal hormones, especially progestogen, probably act by accelerating existing tumors in the breast. Once we get the life course biology right, the pharmacological role on disease prevention will mean massive opportunities (and mass markets). Hormone replacement therapy shows that good intentions can be seriously misleading; hence adequate, as opposed to merely plausible, science is required. Prof John Bailar of the University of Chicago reminds us, "We never know as much as we think we do."

[22]Meanwhile, women with menopausal symptoms have to make decisions. In today's BMJ a clinical net benefit analysis provides insight by balancing current benefit for symptoms against future benefit and risk. [23]It is one way of combining the risks and benefits of future events while ameliorating current discomfort. The latest risk estimates are combined with qualityoflife weightings associated with symptoms for women aged 50. This kind of analysis is essential but inevitably aggregated and somewhat static. However, the effects assumed for breast cancer and coronary heart disease are probably too conservative (because so many women in the trial stopped treatment). A relative risk of breast cancer of around two for combined treatment would considerably decrease the reported chance of net benefit compared with the 1.27 assumed. Similarly, a near doubling of risk of coronary heart disease in the first year would make things still worse, from an assumed overall relative risk of 1.08. These higher risk values would make the probability of net harm considerably greater for any woman.

Combined hormone replacement therapy is not indicated for women who have no symptoms. Only with severe symptoms (the consequent reductions in quality of life are such that a woman would sacrifice three months in a year to eliminate them) do these analyses show the net benefit with

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hormone replacement therapy to be positive. Taking hormone replacement for moderate symptoms require special justification if an average women wishes to benefit in the long run. Menopausal symptoms and risk of breast cancer will always dominate women's decisions, while successfully preventing osteoporosis requires long term use of hormone replacement therapy and cannot be justified by the greater interim hazards of doing so.

We will be increasingly invited to play up the risks of the diseases against which hormone replacement offers effective and downplay the increased risks. As is already the case, we are invited to believe that the women's health initiative study[24]and the million women study are less relevant than is currently thought or flawed with biases. Subgroups will be cited for which the bad effects are not observed—the latest results on coronary heart disease from the women's health initiative study provide (unsafe) opportunities to cite subgroups for which the bad effects are not observed.[25]This is a predictable bandwagon effect, not to be ignored—but such claims are often not plausible, never mind adequate. Reputations (and money) are at stake. Where is the scientific evidence for alternative inferences, more reliable than we now have? That the simple message above, intuitive to public health a while ago, has had to wait to achieve credibility is pitiable.

At least two further developments are now indicated. One is providing hormone therapy with which it is easier to cut the dose gradually. Women can test their individual metabolic balances with progressively lower doses and presumably thereby lower their risk of breast cancer and cerebrovascular disease. As it is, patches and pills can often be cut—but what is required is a product for achieving the lowest doses that can be found to combat symptoms with fewest side effects.

Further, the increased availability of natural remedies that do not need licences requires care with efficacy and safety. If they work for some, fine, but evidence from trials would be essential for women to be assured that they pose no greater risks than hormone replacement therapy. Safety data are vital for products whose constituents are not necessarily entirely known and that may contain, for example, phytoestrogens in large doses. What are the longterm effects of these preparations, taken on the assumption that being natural they are safe? Will adequate research be done to ensure that we avoid another half century of uncontrolled experimentation on menopausal women? Women have greater expectations of menopausal remedies now—given the false promise of the hormone replacement therapy bandwagon.

It can take decades to detect important and unanticipated side effects of medications reliably. Do the current regulatory provisions adequately provide for the sensible avoidance of more, tragic episodes? Tucker conservatively estimates an extra 1400 cases of breast cancer, 1200 cases of heart disease, and 1400 cases of stroke—against 860 fewer hip fractures and 1000 fewer cases of colorectal cancer per year in the United States alone.[26]Regulators and legislators will be contemplating the implications, as they did after thalidomide, and hopefully we will not get the marketing so wrong again. Severe menopausal symptoms are rated as having worse effects on quality of life than having any of the diseases—pills for symptoms and prevention pose complicated public health problems. Hormone replacement therapy may be a mere example of what is to come—the opportunities remain enormous.

CLASSIFICATION[26]

- MENOPAUSE HORMONE REPLACEMENT THERAPY

It is important to review the goals of hormone-replacement therapy (HRT)—for example, treatment of menopausal symptoms vs prevention of osteoporosis—with the patient before initiating therapy (table 1)

Efficacy of HRT should be assessed after 4 to 6 weeks; doses can be titrated upward until symptoms are relieved. The need for continued therapy can be evaluated every 4 to 6 monthsHRT may be given orally, transdermally, or intravaginally in either continuous or cyclical schedules

Progesterone is usually given with estrogen for women with a uterus to prevent endometrial hyperplasia. Women without a uterus do not require progesterone. Uterine bleeding that is excessive, prolonged, or in any way different from the expected bleeding of the prescribed regimens must be evaluated promptly with endometrial biopsy, ultrasonography, or both. Premenstrual-like symptoms (breast tenderness, bloating, mood swings, headache) can occur when HRT is initiated. Many resolve spontaneously within a few months. Lowering the progesterone dose or switching from cyclical to continuous HRT can help**TABLE 1: SUMMARY OF HORMONE**

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REPLACEMENT THERAPY TREATMENT EFFECTS [26]

Condition	Estrogen alone	Estrogen and progesteron	Rolaxifen HCl	Estrogen and progesteron	biphosphates
Hot flashes and urogenital symptoms	++	-	++	-	00
Mood, cognitive libido changes	+	+	00	+	00
Osteoporosis	++	++	++	++	++
Coronary artery disease	+/-	+/-	0	0	00
Stroke	00	-	0	0	00
Breastcancer	-	-	++	0	00
Endometrial cancer	–	00	00	0	00
Deep venous thrombosis or pulmonary embolus	--	--	--	0	00

- **Growth Hormone Replacement Therapy**

[27]Adults with growth hormone deficiency (GHD) receiving adequate growth hormone replacement therapy have decreased mortality risk when compared with historical groups of patients with untreated GHDThe results of the study, say the researchers, support the idea that long-term growth hormone replacement therapy is safe in this patient population.

GHD, as a component of hypopituitarism, is associated with increased mortality. Smaller-scale studies showed that patients with GHD receiving growth hormone replacement therapy still have mortality rates superior to those in the general population. The precise influence of this therapy on mortality in patients with GHD has not, however, been extensively studied.

Gaillard et al. analysed the medical records of a cohort of nearly 14,000 patients with GHD who were receiving growth hormone replacement therapy and were registered in KIMS, the Pfizer International Metabolic Database. The researchers determined risk factors for increased mortality in this patient population and also aimed to evaluate the effect of growth hormone replacement therapy on mortality rate.

In comparison with data from a general reference population, the all-cause mortality rate was increased by 13% in the studied patients, which is a lower increase than that previously reported for patients with untreated GHD. In line with the results of previous studies, diagnoses of craniopharyngioma, aggressive sellar or brain tumour, Cushing disease or diabetes insipidus were risk factors significantly associated with an increased mortality rate, as well as female sex and young age.

"We could not compare treated patients with those who did not receive growth hormone therapy using this cohort," explains Roger Abs, senior investigator at the Antwerp Centre for Endocrinology, "so we used a measurement of insulin-like growth factor I (IGF-I) level as a marker". A low IGF-I level, indicative of insufficient growth hormone replacement, was associated with increased mortality risk.

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Although cardiovascular disease and cancer were the leading causes of death among the studied patients, no significant differences in mortality as a result of these diseases were observed between the patients and the reference population.

The mortality rate might be lower in this cohort as a consequence of increased surveillance. Nevertheless, "on the basis of these data, growth hormone replacement can be considered a safe treatment in adults with GHD.

- **TESTOSTERON REPLACEMENT THERAPY**

[28]Testosterone has many beneficial effects, including increasing bone strength and density, inducing hematopoiesis, driving sexual function and libido, providing a cardioprotective effect and increasing muscle strength.[29]Testosterone levels are known to decline as men age. The Baltimore Longitudinal Study of Aging reported the incidence of hypogonadism as 20% in men over 60 years of age, 30% in men over 70 years and 50% in men over 80 years of age.

[30]As men age, a decline in testicular production of testosterone are seen, as well as an increase in sex hormone binding globulin, both of which act to decrease bioavailable testosterone. [31]With this gradual decline, the beneficial effects of testosterone could be diminished and negatively affect physical and emotional well-being. Testosterone replacement therapy (TRT) is a reasonable treatment option often discussed for men with low testosterone levels and symptoms of hypogonadism. When replaced, many of the positive effects of testosterone are regained. [32]These positive results have led to a drastic increase in the use of testosterone replacement for men with symptomatic hypogonadism, though long-term data is lacking on the safety.

While the beneficial effects of testosterone are rarely disputed and widely publicized, there is a paucity of the literature on the risks of testosterone use. Any man who has a comorbidity that precludes TRT should be informed of all risks. Factors such as exacerbation of prostate cancer, male breast cancer, worsening benign prostatic hyperplasia (BPH), polycythemia and an increased risk of obstructive sleep apnea (OSA) should be considered when administering TRT to a patient. The goal of this review is to highlight the risks and summarize the current literature on safety of TRT.

- **THYROID HORMONE REPLACEMENT THERAPY**

Hypothyroidism is common throughout the world and readily diagnosed with thyroid function tests. Management should be straightforward but appears not to be the case. Thyroid hormone replacement with levothyroxine monotherapy is the standard treatment which is effective in the majority of cases. However, 10–15% of patients established on levothyroxine do not feel their health is entirely restored and some patients prefer the addition of liothyronine. Proponents of liothyronine argue that the ratio of T3 and T4 hormones is substantially altered on T4 monotherapy and therefore both hormones may be needed for optimal health. This remains controversial as clinical trials have not demonstrated superiority of combination therapy (levothyroxine and liothyronine) over levothyroxine monotherapy. There is now a pressing need for further studies and in particular randomized controlled trials in this area. To help design and facilitate dedicated trials and better understand thyroid hormone replacement, this review summarizes the evidence where there is established knowledge and agreement (knowns) and areas where research is lacking (unknowns). Agreements include the extent of dissatisfaction with levothyroxine monotherapy, biases in testing for hypothyroidism and prescribing levothyroxine, as well as variable thresholds for prescribing levothyroxine and challenges in liothyronine dosing. The review will also highlight and summarize the unknowns including the long-term safety profile of liothyronine, and potential biomarkers to identify individuals who might benefit most from combination therapy.[33]

- **WAYSOF TAKING HRT**

HRT comes in several different forms. Talk to a GP about the pros and cons of each option.

Tablets

Tablets are 1 of the most common forms of HRT. They are usually taken once a day.

Both estrogen-only and combined HRT are available as tablets. For some women this may be the simplest way of having treatment.However, it's important to be aware that some of the risks of HRT, such as blood clots, are higher with tablets than with other forms of HRT (although the overall risk is still small).

Skin patches

Skin patches are also a common way of taking HRT. You stick them to your skin and

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replace them every few days.estrogen-only and combined HRT patches are available.Skin patches may be a better option than tablets if you find it inconvenient to take a tablet every day.Using patches can also help avoid some side effects of HRT, such as indigestion, and unlike tablets, they do not increase your risk of blood clots.

estrogen gel

estrogen gel is an increasingly popular form of HRT. It's rubbed onto your skin once a day.Like skin patches, gel can be a convenient way of taking HRT and does not increase your risk of blood clots.But if you still have your womb, you'll need to take some form of progestogen separately too, to reduce your risk of womb cancer.

Implants

HRT also comes as small pellet-like implants that are inserted under your skin (usually in the tummy area) after your skin has been numbed with local anaesthetic.The implant releases estrogen gradually and lasts for several months before needing to be replaced.This may be a convenient option if you do not want to worry about taking your treatment every day or every few days. But if you still have your womb, you'll need to take progestogen separately too.If you're taking a different form of estrogen and need to take progestogen alongside it, another implant option is the intrauterine system (IUS). An IUS releases a progestogen hormone into the womb. It can stay in place for 3 to 5 years and also acts as a contraceptive.Implants of HRT are not widely available and are not used very often.

Vaginal estrogen

Estrogen is also available as a cream, pessary or ring that is placed inside your vagina.This can help relieve vaginal dryness, but will not help with other symptoms such as hot flushes.It does not carry the usual risks of HRT and does not increase your risk of breast cancer, so you can use it without taking progestogen, even if you still have a womb.

Testosterone

Testosterone is available as a gel that you rub onto your skin. It is not currently licensed for use in women, but it can be prescribed after the menopause by a specialist doctor if they think it might help restore your sex drive.Testosterone is usually only recommended for women whose low sex drive (libido) does not improve after using HRT. It is used alongside another type of HRT.Possible side effects of using testosterone include acne and unwanted hair growth.Ask a GP for more information on testosterone products.

HRT treatment routines

Your treatment routine for HRT depends on whether you're in the early stages of the menopause or have had menopausal symptoms for some time.The 2 types of routines are cyclical (or sequential) HRT and continuous combined HRT.

Cyclical HRT

Cyclical HRT, also known as sequential HRT, is often recommended for women taking combined HRT who have menopausal symptoms but still have their periods.

There are 2 types of cyclical HRT:monthly HRT – you take estrogen every day, and take progestogen alongside it for the last 14 days of your menstrual cycle. Monthly HRT is usually recommended for women having regular periods.

3-monthly HRT – you take estrogen every day, and take progestogen alongside it for around 14 days every 3 months3-monthly HRT is usually recommended for women having irregular periods. You should have a period every 3 months.It's useful to maintain regular periods so you know when your periods naturally stop and when you're likely to progress to the last stage of the menopause.

Continuous combined HRT

Continuous combined HRT is usually recommended for women who are postmenopausal. A woman is usually said to be postmenopausal if she has not had a period for 1 year.Continuous combined HRT involves taking estrogen and progestogen every day without a break.estrogen-only HRT is also usually taken every day without a break.

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